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Archives of Internal Medicine

VOLUME 55 JANUARY 1935 NUMBER 1

SYMPTOMATOLOGY OF MYXEDEMA

ITS RELATION TO METABOLIC LEVELS, TIME INTERVALS AND RATIONS OF THYROID

J. H. MEANS, M.D.
AND
J. LERMAN, M.D.
BOSTON

Our excuse for introducing for discussion so time-worn a subject as the symptomatology of myxedema is that the recent introduction of artificial hypothyroidism as a form of therapeutics makes the topic once more timely. If one is to steer successfully between the Scylla of congestive heart failure or angina pectoris on the one hand and the Charybdis of myxedema on the other, some precise information concerning the relation of symptoms to metabolic rates, time intervals and thyroid rations becomes necessary. Coordinated clinical observations and determination of the metabolic rate on patients with myxedema have been accumulating in our clinic over a period of twenty years (more than two hundred and forty cases). This material provides an excellent source of information. Many of our patients have been under observation year after year, so that our estimate of the relation of symptoms to the height of the metabolic rate is based on long periods in which the level has been steady.

Recently we saw our first patient with myxedema, Mrs. D., whose case was reported fully by Means and Aub [1] in 1919 and who first came under observation in October 1914, when she was 57 years old. She had then had myxedema for six years, but had taken no treatment. For just less than twenty years she has steadily received a thyroid ration and has remained essentially in perfect health. When we saw her on April 3, 1934, she was an alert, active woman of 77.

During this rather prolonged period of observation of patients with myxedema certain facts have strongly impressed us. One is that the people in whom the disease spontaneously develops possess, for the most part, what Draper [2] might call a characteristic physical and mental panel.

From the Thyroid Clinic of the Massachusetts General Hospital.

Read before the Association of American Physicians, Atlantic City, N. J., May 2, 1934.

1. Means, J. H., and Aub, J. C.: The Basal Metabolism in Hypothyroidism, Arch. Int. Med. **24**:404 (Oct.) 1919.

2. Draper, G.: Disease and the Man, New York, The Macmillan Company, 1930.

Physically they tend to be broad-shouldered, short-necked and stocky. Mentally they are characterized by a sunny disposition and fine sense of humor. They are what the Victorians would have called amiable—amazingly so.

For the purposes of the present study, fifty of the group were made the subject of careful scrutiny. The facts which emerged have been sublimated in chart 1. This figure is a generalization. It portrays approximately what happens in most cases, not precisely what happens, unless by chance, in any single case. It shows, we believe, with a fair

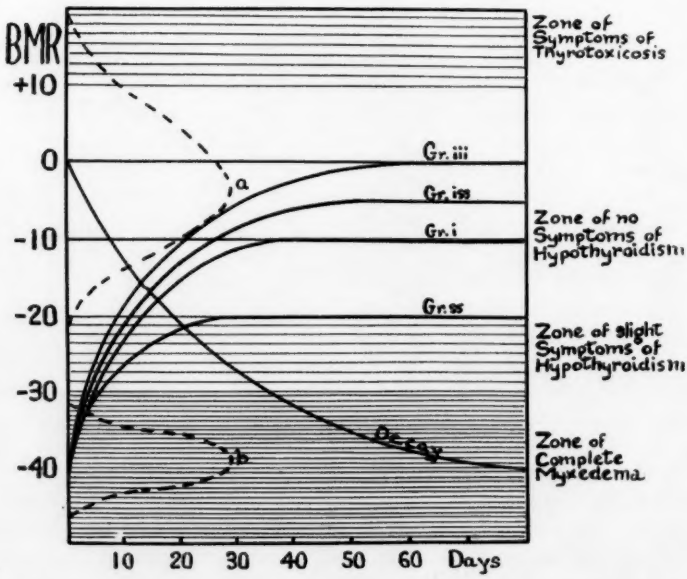

Chart 1.—Diagram showing the approximate relationships between metabolic levels, symptoms and thyroid rations. The dosage is indicated in grains of thyroid, U. S. P., given once a day. The curves, so labeled, indicate what may be expected to happen in the way of calorigenic response when the several rations are given to patients with complete myxedema. The curve labeled decay indicates the metabolic response which may be expected when one discontinues the administration of thyroid to a patient with myxedema whose metabolic rate was maintained at a standard level or when one completely extirpates the thyroid gland of a person with a standard metabolic rate. The frequency curves, plotted against the basal metabolic rate, at the left are (*a*) for persons with no thyroid disease and (*b*) for patients with spontaneous myxedema.

degree of accuracy, the results that one may expect in treating patients with hypothyroidism and how to employ symptoms as a guide.

In the first place, it became clear that the true basal metabolic level of untreated patients with fully developed myxedema is far more constant than that of persons with intact thyroid glands. Epstein [3] called attention to this fact and referred to the metabolism of the person with no thyroid gland as the true biologic basal or "fundamental" metabolism, a foundation on which all higher rates are erected. We agree. On the left side of chart 1, plotted against the metabolic rate, are two frequency curves, showing the basal metabolic rates (*a*) of persons with no thyroid disease and (*b*) of persons with myxedema. It will be noted that *a* has a far wider base than *b*. That is to say, the basal metabolic rates of persons with an intact thyroid gland are far more variable than those of persons with no thyroid gland.

The next point of interest is that the presence or absence of symptoms is closely related to the level of metabolism. In chart 1 are shown several zones which indicate the general nature of the relationship. Below minus 30 (speaking always in terms of the Aub-DuBois standards) is the zone of complete myxedema. One seldom finds fully developed symptoms of hypothyroidism unless the metabolic rate has entered this region. The converse is not true, as will be noted later, because the metabolic rate falls more rapidly than symptoms develop. From minus 20 to minus 30 is the region in which one usually finds slight symptoms of hypothyroidism. Above minus 20 one seldom observes them. When the metabolic rate has been forced upward by the administration of thyroid to the neighborhood of plus 10, symptoms of hyperthyroidism not infrequently make their appearance.

We have given special attention to the problem of the level at which a given ration of thyroid will hold the metabolic rate of patients with myxedema. The four curves shown in chart 1 indicate our experience. The dosage is in terms of thyroid, U. S. P. This must be emphasized, because the brands of thyroid on the market do not all conform to the requirements of the pharmocopeia for iodine and therefore differ in calorigenic action.[4] The ascending limbs of the curves indicate, in days, approximately the time required for the metabolic rate to become steady. The curves are smoothed from the numerous assays we have made of thyroid preparations. The levels themselves are taken from the observations on patients treated for a long time. The results show that ½ grain (32.4 mg.) of thyroid once a day will maintain the basal rate of most patients with myxedema at a level of about minus 20,

3. Epstein, A. A.: The Reciprocal Functions of the Thyroid Gland and Iodine: Their Relation to the Fundamental Metabolism of the Body, Libman Anniversary Volumes, New York, International Press, 1932, vol. 1, p. 365.

4. Lerman, J., and Salter, W. T.: The Maintenance Requirements of Myxedema Patients: Clinical and Chemical Assay of Commercial Thyroid Preparations, J. Pharmacol. & Exper. Therap. **50**:298, 1934.

which, it should be noted, is about the upper border of the zone of slight symptoms. One grain (64.8 mg.) maintains the rate at about minus 10, 1½ grains (97.2 mg.), at about minus 5, and 3 grains (194.4 mg.), at about the standard level.

For comparison we have inserted also in chart 1 the so-called curve of decay of the hormone. This represents the effect on the metabolic rate of sudden elimination of the source of thyroxine. It is what may be expected if one suddenly stops the thyroid ration of a patient with myxedema whose rate has been maintained at a standard level, or if the thyroid gland is completely extirpated. There are a number of such curves in the literature,[5] and they are surprisingly alike in contour. The important point about them is that it takes seventy or more days to attain the metabolic level of complete athyreosis.

The nature of the curve of decay led to a study of the rate of development of symptoms. Regarding this, some interesting points were found. We had been aware for a number of years, as doubtless had others doing the same sort of work, that in the development of the picture of hypothyroidism the fall in the metabolic rate precedes the development of clinical symptoms and signs. For example one patient (Mrs. B.) who was first seen with fully developed myxedema was given 10 mg. of thyroxine in one dose intravenously, for purposes of assay. This raised the basal metabolic rate from a level of minus 45 to one of about minus 6 in seven days. The metabolic rate was back in the minus thirties within a month, but it was about three months before any symptoms of importance appeared. This result was duplicated in several other patients, and is similar to the effect observed in artificial hypothyroidism.[6] This lag of symptoms behind the change in the metabolic rate is probably to be explained by the fact that although the symptoms and the metabolic rate are unquestionably related, the symptoms are due in large measure to the lack of other than the calorigenic action of thyroxine. Indeed, with the evidence now at hand, it seems unlikely that more than chilliness and decreased sweating can be explained by a low metabolic rate alone. The other signs of classic

5. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, Tr. A. Am. Physicians **40**:195, 1925. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: The Calorigenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, J. Clin. Investigation **7**:437, 1929.

6. Gilligan, D. R.; Volk, M. C.; Davis, D., and Blumgart, H. L.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: VIII. Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism, Arch. Int. Med. **54**:746 (Nov.) 1934.

myxedema have to do with other actions of thyroxine, for example, its action on the distribution of body water, salt and protein and on the rate of growth of the tissues.

In the matter of symptoms of spontaneous myxedema, we became convinced that truly full-blown athyreotic cachexia requires a long period of time to develop. After the metabolic rate drops into the zone of symptoms, a slow evolution takes place over a period of years. Since in spontaneous myxedema the lesion found is total atrophy of the thyroid gland, one must infer that in the beginning of the disease a period of partial athyreosis exists. However, experience with induced athyreosis shows that myxedema is not produced unless the gland is totally removed: A small fragment is capable of supplying an adequate or nearly adequate amount of thyroxine. Therefore, it may fairly be inferred that the symptoms of spontaneous myxedema come on only after the atrophy of the gland has become complete. The period of partial athyreosis is passed in the asymptomatic zone of metabolism.

Though once in a great while a person may be found with a moderately low basal metabolic rate, say minus 20, in whom true myxedema is actually developing, for the most part persons with such a rate do not have hypothyroidism but owe their low metabolic rate to some other mechanism. We interpret our experience as signifying that a person either does or does not have myxedema. Borderline or halfway types of hypothyroidism, we think, exist either not at all or rarely. Hypometabolism is no more synonymous with hypothyroidism than fever is synonymous with measles. Indeed, we have had patients with a metabolic rate as low as minus 40 who did not show clinical signs of myxedema and whose low rate was in all probability not related to disturbance in the thyroid gland.

The length of time required to make the diagnosis of myxedema next engaged our attention. It is unfortunate when the diagnosis of a curable disease is missed, particularly if, when untreated, it ultimately causes death, as is the case with myxedema. In forty-three of the fifty cases analyzed the history permitted an estimate of the length of time the disease existed before the diagnosis was made. These data are given in chart 2. Two patients undoubtedly had myxedema for fifteen years before it was recognized. One of them was seen last winter in consultation with Dr. J. H. Townsend at the Cambridge Hospital. She was a woman who was brought to the hospital for the first time in a lethargic state, nearly moribund. Dr. Townsend recognized the condition as myxedema and invited us to see her. Thyroxine was given intravenously but it was too late; she died within twelve hours after treatment was begun. The diagnosis of myxedema should be easy, but chart 2 indicates that nevertheless it often is missed. Of the wrong diagnoses made in these cases, anemia was first, then Bright's disease. In two cases, because

of menorrhagia (which is the characteristic menstrual change in women in whom myxedema develops prior to the menopause) a diagnosis of pelvic tumor was made, and the patients sent to a hospital for gynecologic diseases for operation. At this hospital the right diagnosis was made, and the patients were sent to us. In a third recent case, not included in this series, there was a history of hysterectomy for menorrhagia. The circumstances were such that we suspected that the menorrhagia was caused by myxedema and that the hysterectomy was not necessary.

We hope that the information contained in chart 1 may be helpful in the management of either spontaneous or induced hypothyroidism. It

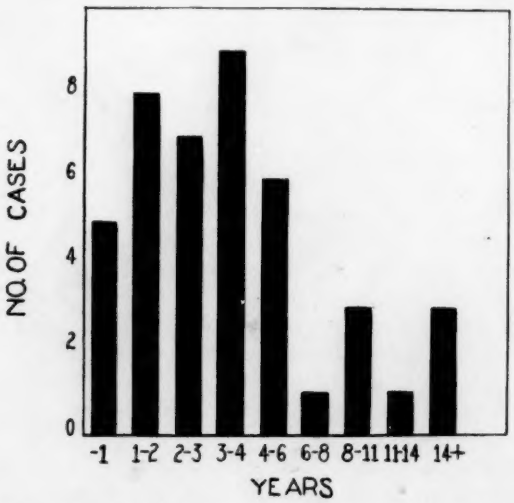

Chart 2.—Time elapsing in cases of myxedema before a diagnosis was made as estimated in forty-three cases.

is perhaps more instructive in relation to the latter condition. It provides an answer to the question so commonly asked: "What is the sense of removing the thyroid gland to cure heart disease when it will cause myxedema and make the heart worse?" The diagram indicates that if the metabolic rate of the patient with cardiac disease is at the standard level or higher, a 20 or 25 point drop can be effected with little or no symptoms of hypothyroidism. This may be sufficient to make the difference between cardiac decompensation and compensation. A method may some day be found to lower the metabolic rate to minus 40 without producing myxedema; then the patient with cardiac disease may rejoice. At the moment the patient may be thankful for the 20 point drop in the rate which is now possible.[6]

GASTRIC MUCIN TREATMENT FOR PEPTIC ULCER

A REPORT BASED ON QUESTIONNAIRES

SAMUEL J. FOGELSON, M.D.
CHICAGO

My interest in the rôle played by mucin in the physiology of the gastro-intestinal tract and the management of gastroduodenal ulceration was stimulated by Lim's publication, "On the Relationship Between the Gastric Acid Response and the Basal Secretion of the Stomach."[1] At the lower secretory rates the concentration of mucus is undoubtedly higher than during the more active phases of gastric secretion. Many clinicians have noted a decreased secretion of mucus in patients with ulcer.[2] It is likewise noteworthy that the many patients with ulcer rarely return to a normal basal secretory state. My objective, therefore, was to feed mucin to patients with ulcer in an attempt to correct the mucin deficiency as well as to restore normal basal secretory rates. By 1929 I had prepared a gastric mucin adequate for experimental and clinical investigation. The first clinical report on the treatment of gastroduodenal ulceration with gastric mucin followed in 1930, when the encouraging results in 12 patients were described.[3] Experimental investigation by Ivy[4] on the control of experimental ulcer by mucin followed, affording further physiologic support for continuing my clinical research on the management of peptic ulcer with gastric mucin.

To obtain an accurate evaluation of mucin as well as to eliminate personal bias, there was established by the Northwestern University Medical School a Gastric Mucin Committee. Under the direction of this committee the following units were established for the investigation of the treatment of gastroduodenal ulcerative disease with mucin: at St. Luke's Hospital, Chicago, under the direction of Dr. N. C. Gilbert and Dr. C. F. G. Brown;[5] at the Passavant Hospital, Chicago,

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From the Department of Experimental Surgery, Northwestern University Medical School.

1. Lim, R. K. S.: On the Relationship Between the Gastric Acid Response and the Basal Secretion of the Stomach, Am. J. Physiol. **69**:318 (July) 1924.

2. Kaufman, J.: Lack of Gastric Mucus and Its Relation to Hyperacidity and Gastric Ulcer, Am. J. M. Sc. **135**:207, 1908.

3. Fogelson, S. J.: The Treatment of Peptic Ulcer with Gastric Mucin, J. A. M. A. **96**:673 (Feb. 28) 1931.

4. Ivy, A. C.: The Physiology of Mucous Secretion with Some Experimental Results on the Prevention of Ulcer with Gastric Mucin, Nebraska State M. J. **17**:317 (Aug.) 1932.

5. Brown, C. F. G.; Cromer, S. P.; Jenkinson, E. L., and Gilbert, N. C.: Mucin Therapy for Peptic Ulcer, J. A. M. A. **99**:98 (July 9) 1932.

under the direction of Dr. A. J. Atkinson,[6] and at the Wesley Memorial Hospital, Chicago, under my own charge. These three groups treated over 600 patients with encouraging results, confirming, in general, my original report.

In addition, mucin was made available to all physicians interested, with the request that they cooperate with the Gastric Mucin Committee in reporting the type of condition treated and the results obtained. The present report, based on the results obtained by clinicians with little or no previous experience with mucin therapy, should be valuable in determining the effectiveness of mucin therapy.

DATA FROM QUESTIONNAIRES ON 555 CASES

During the last three years there have been reported to the Gastric Mucin Committee approximately 555 patients who have been followed for periods varying from six months to three years. These patients were divided into two groups: (1) a group of patients in whom it had been possible to control the symptoms by the accepted orthodox methods, and (2) another group in which the types of therapy previously used afforded no relief. The cases in the latter group were classified as "intractable." The committee decided that unless mucin should prove of value in the treatment of this group with "intractable" cases of ulcer, it deserved no place in the medical management of ulcer and that its manufacture as well as its distribution would be stopped. To simplify the treatment all clinicians interested in this work were supplied with instructions, describing the dosage as well as the simplest and most effective technics of administration of mucin. To facilitate the reporting, these clinicians were likewise furnished summary sheets for a brief history stressing classification of the type of lesion treated, the roentgenographic findings, the history of recurrences, the incidence of hemorrhage, previous surgical procedures and the effect of former treatment. The results obtained with mucin therapy were recorded on a progress sheet which included the more significant symptoms and the time required for their control. Table 1 shows a typical progress record from a clinician cooperating in this study.

Much valuable information was acquired about effective dosage, the mode of administration and the occurrence of unfavorable effects. Such data were of real value in determining just what results may be expected from mucin therapy in the treatment of patients with ulcer, particularly of patients who previously did not respond to medical management or to surgical therapy. Practically no patients were hos-

6. Atkinson, A. J.: Gastric Mucin in the Treatment of Peptic Ulcer, J. A. M. A. **98**:1153 (April 2) 1932.

TABLE 1.—*Report Showing Typical Response to Mucin Therapy by Patient with Uncomplicated Gastric Ulcers* *

Place + or 0 in square depending on the presence or absence of symptom. Diagnosis: Gastric ulcer Date of monthly report: May 12, 1932

Name of Patient: E. L. Name of Physician: C. L. A., Ville Platte, La.

1932	April																		May										
Day of month	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12
Time of mucin treatment	100 Gm. daily in 1½ quarts milk and cream divided into 12 hourly doses																														
Nausea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pyrosis	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eructation	0	0	0	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Belching	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Flatulence	+	+	+	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Epigastric pain	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Epigastric discomfort	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Epigastric tenderness	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	+	+	+	+	+	+	+	+	+	+	0	0	0	+	+	0	0	0	0	+	0	0	0	0	0	+	+	0	0	0	0
Nocturnal pains	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hunger pains	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Constipation	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	+	+	+	0	0	+	0	0	0	0	+	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hematemesis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Melena (benzidine)	+	+	+	+	+	+	0	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastric analysis:																															
Free hydrochloric acid	50						40								35					30									25		
Total acids	90						60								55					55									55		
Red blood count	3,500,000																												4,000,000		
Hemoglobin	70%																												75%		
Weight	130						133								135					136									140		
Belladonna dose	None given																														

* This is the type of record used by the cooperating clinicians in sending to the Gastric Mucin Committee reports on the progress of their patients.

pitalized, because previous experience with ambulatory treatment had proved relatively satisfactory. Patients were instructed to take mucin suspended in a mixture of milk and cream at frequent regular intervals throughout the day. As a rule the average patient can tolerate from 80 to 100 Gm. of dry mucin powder, which to acutely ill patients was administered in hourly doses. Whenever possible the administration of mucin was continued for at least six months, the dosage being reduced during the last three months.

The difficulties of taking mucin by the patient with ulcer have been grossly exaggerated. With no personal experience on their part, the physicians of the 555 patients, following the instruction sheets furnished by the Gastric Mucin Committee, reported no grave difficulty in the protracted administration of the product. To prescribe mucin without proper instruction as to how it is to be taken is to tempt failure. When in doubt, my patients are given a demonstration by a competent dietitian, taste the mixture properly prepared and thus are psychologically prepared against failure. The diet was limited to the customary bland diet for patients with ulcer. Complicating gastro-intestinal conditions such as spastic colitis or constipation were treated by appropriate measures.

RESULTS

The response to mucin therapy was classified as: (1) complete relief of symptoms; (2) partial relief, and (3) absolute failure. Recurrences were included in the group of failures because temporary alleviation of symptoms could hardly be considered more than a frank failure. The reports on a total of 555 patients with an average duration of symptoms of slightly less than eight years were submitted to the Gastric Mucin Committee by clinicians cooperating in this investigation. The greater number of the patients had responded unsatisfactorily to previous therapy; 106 had been submitted to surgical procedures with postoperative recurrence of symptoms, and 220 gave a history of repeated massive hemorrhages. Of the 555 patients treated for periods varying from six months to three years, 348, or 62.7 per cent, were rendered free of symptoms, 114, or 20.5 per cent, were partially improved and 93, or 16.8 per cent, failed to be relieved. In the group of 93 patients who failed to respond to mucin therapy, there were 32 true failures or recurrences. The remaining 61 were patients who for various reasons would not continue the treatment for an adequate period or in whom complicating factors prevented the possibility of obtaining symptomatic relief. Deducting these 61 patients from the total, there remain 494, of whom 348, or 70.5 per cent, were completely relieved of all symptoms, 114, or 23 per cent, were improved and 32, or 6.5 per cent, failed to be relieved.

The types of ulcer treated were as follows:

	No. Patients
Duodenal ulcers	408
Gastric ulcers	125
Gastrojejunal ulcers	22

One hundred and six patients had had previous operations followed by recurrences and 220 had had previous hemorrhage. In some of these patients an occasional symptom persisted for months after the beginning of treatment with mucin, but as a general rule all symptoms were completely controlled within one week.

Group with Intractable Ulcer.—Of the 555 cases, 226 were classified as intractable by the patients' own clinicians because they did not respond to the orthodox types of treatment. Surgical treatment had

TABLE 2.—*Duration of Symptoms After Institution of Mucin Therapy**

Symptoms	Days
Nausea	3.1
Vomiting	1.2
Pyrosis	5.6
Epigastric pain	6.9
Nocturnal pain	5.9
Hunger pain	4.5

* This includes 420 successfully treated patients with ulcer who were under observation for from six to thirty-six months, but does not include 42 intractable cases in which some symptoms persisted in varying degrees for months.

given temporary or no relief of symptoms to 69. In the group of 226 patients with intractable ulcers, 137, or 60.6 per cent, were rendered free from symptoms on mucin therapy; 64, or 28.3 per cent, were partially improved and there was failure or recurrence in 25, or 11.1 per cent, shortly following temporary relief of symptoms. Correction of the total of 226 by the exclusion of 9 in whom complications or failure to continue with mucin therapy for an adequate period precluded the possibility of obtaining symptomatic relief would leave a total of 217 patients; 137, or 63.1 per cent, were relieved of all symptoms; 64, or 29.4 per cent, were partially improved, and 16, or 7.5 per cent, failed to obtain relief. The most significant results were obtained in the patients who had had a previous gastro-enterostomy, and who presented symptoms suggestive of an ulceration at the gastro-enterostomy stoma or of an exacerbation of the original lesion. The failure of the customary orthodox medical management to relieve this type of patient is so well known that additional surgical therapy is usually urged in order to prevent an extension of the existing pathologic condition. In 56 patients with a recurrence of symptoms after

TABLE 3.—*Report Showing Recurrence of Symptoms in the Intractable Case of Duodenal Ulcer*

Place + or 0 in square depending on the presence or absence of symptom. Diagnosis: Duodenal ulcer Date of monthly report:

Name of Patient: R. H. Name of Physician: B. W. S., Louisville, Ky.

1932 Oct.		Nov.				Dec.				Jan. 1933					Feb.				March				April				May		
Day of month	19	26	3	10	17	27	3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17	24	31	7	14	21	28	6*	13†	20
Time of mucin treatment	100 Gm. daily in 12 hourly doses						100 Gm. in 6 daily doses at 2 hour intervals																								
Nausea	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	+	+	+	+	..	0
Vomiting	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	+	+	+	+	..	0
Pyrosis	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Eructation	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Belching	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Flatulence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Epigastric pain	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	+	+	+	+	+	..	0
Epigastric discomfort	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	+	+	+	+	+	..	0
Epigastric tenderness	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	+	+	+	+	+	..	0
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Nocturnal pains	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Hunger pains	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	..	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hematemesis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Melena (benzidine)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastric analysis:																															
Free hydrochloric acid	62																												54		
Total acids	72																												68		
Red blood count																															
Hemoglobin																															
Weight	168			175			177			180										189					183						
Belladonna dose																															

* Roentgenogram of May 6, 1933, showed a definite penetrating duodenal ulcer.
† Resection of pylorus.

a gastro-enterostomy, it was possible to obtain complete control of all the subjective symptoms in 36, partial relief in 16 and no relief in 4. To this group may be added 13 additional patients who had had operations other than gastro-enterostomy, and in whom symptoms had recurred. Ten patients in this group were relieved completely by mucin therapy, 1 was partially improved and 2 failed to obtain relief.

Failures.—There was a total of 93 failures, which included 61 patients who may be properly excluded because they either stopped the mucin therapy before its effect could be determined or persisted in other types of therapy at the same time. Some had complicating conditions such as diabetes, cholecystitis and nephrosis, all of which interfered with the main objective. The 32 unexplainable failures or recurrences after a temporary relief occurred in patients despite attention to all details of the mucin management. Recurrence of symptoms while still receiving mucin in 6 persons with intractable and in 1 person with simple ulcers and the occurrence of perforation in 1 and of acute massive hemorrhages in 4, all unexplainable, emphasize the limitations of mucin therapy (table 3).

COMMENT

Although something is known about the chemistry of mucin much remains to be learned. Mucin is a glucoprotein containing glucuronic acid, known to detoxicate certain substances such as phenol. The toxic substances in question combine with glucuronic acid and are eliminated in the urine as glucuronates. The question whether glucuronic acid is synthesized in the body is disputed. But obviously, if glucuronic acid is not synthesized in the body, and is used excessively for detoxifying purposes, the amount of mucin present would tend to be diminished. It is interesting to note that damage to the liver and gastroduodenal ulcer are frequently associated in the experimental animal. This important phase of mucin chemistry and metabolism is now being investigated by Miller and Crandall.[7]

A chemical quantitative method for following the secretion of mucin has been devised by Farmer and Anderson of the Northwestern University Medical School, and preliminary investigation has suggested a deficiency of mucin in many patients with ulcer, at least during active secretory states. Such a deficiency was observed by Hurst [8] in 10 per

7. Miller, C. O., and Conner, J. A.: Origin of Glucuronic Acid in Urine of Rabbits, Proc. Soc. Exper. Biol. & Med. **30**:630, (Feb.) 1933. Miller, C. O.; Brazda, F. G., and Elliott, E. C.: Studies on Metabolism of Glucuronic Acid in Dog, ibid. **30**:633 (Feb.) 1933. Miller, C. O.; Siehrs, A. E., and Brazda, F. G.: Glucuronic Acid as Growth Factor in Guinea Pigs, ibid. **30**:636 (Feb.) 1933. Crandall, L. A.; Roberts, G. M., and Gibbs, J. W.: The Beneficial Effect of Mucin and Chondroitin in Experimental Liver Damage, ibid. **29**:1082 (June) 1932.

8. Hurst, A. F.: The Unity of Gastric Disorders, Brit. M. J. **2**:89, 1933.

cent of all normal young adults, who he believes are predisposed to the formation of ulcers since they have not only this deficiency of mucus but also hyperchlorhydria and short, high stomachs which empty rapidly. Feeding gastric mucin to these predisposed persons should meet this deficiency and thus serve as a prophylactic therapy against gastroduodenal ulcerative disease.

Physiologists teach that mucus has the function of protection and lubrication. That it lubricates is obvious. That it protects the stomach from autodigestion has been maintained since the time of Spallanzani. Evidence in support of this contention has been presented by Claude Bernard,[9] Schiff,[10] Klug [11] and Whitlow.[12] Whitlow, working with Ivy, confirmed the belief that the mucin-containing cells of the gastric epithelium are the last layer of the gastric wall to be digested by gastric juice, and demonstrated that hydrochloric acid-pepsin diffuses slowly through a film of mucus, and that if the film of mucus covering the mucosa of the pyloric antrum is wiped away the application of tenth-normal hydrochloric acid causes bleeding much sooner than otherwise.

The Pavlov school has held that gastric mucus not only functions as a physical protective substance, but also neutralizes or buffers acid. There exists a conflict of opinion regarding the function of the normally secreted mucus in controlling gastric acidity. This is due to the inability to measure the output of the mucus-secreting cells of the entire stomach during digestion. Bonis [13] and Mitchell [14] found that the buffers of gastric juice are almost entirely dialyzable, indicating that the mucus itself has little buffer value. However, Mitchell observed that 100 cc. of highly buffered mucus is capable of inhibiting the proteolytic action of 40 cc. of gastric juice by a combined neutralizing, diluting and buffering action, and pointed out that this function would be of greatest value under normal conditions after the evacuation of a meal. If one leg of a pithed frog is placed in gastric juice containing a 2 per cent solution of mucin and the other leg is placed in gastric juice without mucin, the latter is digested to a far greater extent than the former.

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9. Bernard, Claude: Leçons la physiologie et la pathologie du système nerveux, Paris, J. B. Baillière et fils, 1856, vol. 2.

10. Schiff, J. M.: Leçons sur la physiologie de la digestion, Paris, H. Loescher, 1867, vol. 2.

11. Klug, de F.: Pourquoi les ferments protéolytiques ne digérent-ils pas l'estomac et l'intestin sur le vivant? Arch. internat. de physiol. **5**:297, 1907.

12. Whitlow, J. E.: The Protective Action of Mucus, master's thesis, Loyola University (unpublished).

13. Bonis, A.: Magenschleim und Säurebindung, Zugleich ein Beitrag zur Titration mit Indikatoren und sur elektrometrischen Titration des Magensafts, Ztschr. f. klin. Med. **113**:611, 1930.

14. Mitchell, T. C.: Buffer Substances of Gastric Juice and Their Relation to Gastric Mucus, J.Physiol. **73**:427 (Dec.) 1931.

This shows that mucin retards, but does not entirely inhibit, the digestive action of gastric juice. With the evidence at hand it can only be stated that: mucus and the mucin-containing cells of the gastric epithelium protect the mucosa from physical and chemical trauma; gastric mucus per se probably plays only a minor rôle in the control of gastric acidity during digestion, and gastric mucin inhibits the action of pepsin in gastric juice.[15]

The iso-electric point of gastric mucin is between p_H 3 and 3.5, the hydrogen ion concentration at which free acid is measured (by Töpfer's test) and at which mucin is least soluble, thus making it most efficient as a chemical and physical protective agent during the active secretory phases. Bucher's investigation on the "Protective Action of Gastric Mucus"[16] confirmed these findings and interpretations. He believed that the problem still to be solved is whether mucus exerts a protective action against the stomach's own juice, and whether a deficiency in this protective action may not be a causal factor in peptic ulcer. Leriche[17] estimated that there are more than 13,000,000 cells in the stomach constantly secreting mucus, which must play an important rôle in gastric physiology. His studies on the staining characteristics of mucus suggests that the fundus is better protected than the antrum by its heavy layer of mucus. He concluded that gastric mucus is of great importance in the physiology and pathology of the stomach and that "mucus of the stomach does not deserve the contempt in which it has been held up to this time."

After preliminary laboratory tests relating to the manufacture and biologic assay of the original gastric mucin, it was thought that no difficulties would be encountered in the manufacturing process. This was found not to be the case. The product varied. Since December 1931, therefore, every batch of the manufactured product has been assayed for (1) its buffer value, (2) its gastric secretogogue value, (3) the presence of irritating amines and (4) its odor and taste. In addition, aerobic and anaerobic bacteriologic counts have been made, and are being made, on the different batches. It has been found that acceptable gastric mucin compares favorably in this respect with certain powdered milks (attempts are being made to prepare a sterile product). If the batches do not meet the requirements of the Gastric Mucin Committee they are rejected.

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15. Babkin, B. P., and Komarov, S. A.: The Influence of Gastric Mucus on Peptic Digestion, Canad. M. A. J. **27**:463, 1932.

16. Bucher, R.: Nature of Protective Action of Gastric Mucus, Deutsche Ztschr. Chir. **236**:485, 1932.

17. Leriche, R.: Necessité d'une systematique de la fonction des glandes à mucus du point de vue de la physiologie, de la pathologie et de la therapeutique, Presse méd. **40**:650 (April 27) 1932.

CONCLUSIONS

1. A study based on questionnaires concerning 494 patients with peptic ulcer treated by clinicians throughout the United States has demonstrated the ability of gastric mucin to control all the symptoms in 70.5 per cent and to afford a partial relief of symptoms in 23 per cent, while failure to afford any relief occurred in 6.5 per cent.

2. In 217 patients with intractable ulcers who could not be relieved of symptoms by medical management, of whom 69 had been submitted to previous surgical procedures, gastric mucin afforded complete relief in 63.1 per cent, partial relief in 29.4 per cent, and no relief in 7.5 per cent.

3. The results obtained in this group of patients with intractable ulcers suggests the possibility of obtaining symptomatic relief with gastric mucin in a relatively high percentage of patients in whom accepted orthodox measures, including operation, have failed.

4. The permanence of the results is not considered, owing to the limited periods of observation.

PARALYSIS OF THE BLADDER IN DIABETIC PATIENTS

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AND
H. H. CRABTREE, M.D.
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INTRODUCTION

Too little attention was paid to neurologic complications and diseases in my group of diabetic patients until Dr. Jordan joined Dr. H. F. Root, Dr. Priscilla White and me in 1930. For the next two and a half years he sought and found much which had been overlooked, disregarded or neglected. Already my associates and I feel indebted to him for his papers on cerebrovascular accidents, convulsions in diabetic patients, neurologic manifestations of hypoglycemia [1]—the two papers which appear in this issue of the ARCHIVES and a forthcoming paper on neuritis. We realize that much of the neurologic field in our practice has been only partially cleared, but we hope that before long the whole of it can be ploughed thoroughly. We regret that following Dr. Jordan's years in Boston and later in Germany, he went to Richmond, Va., but we feel sure that he will continue his painstaking studies of diabetes.

ELLIOTT P. JOSLIN.

Among our diabetic patients we have seen a number with paralysis of the urinary bladder. After the elimination of those cases due to recognized causes of this condition, such as senility, mechanical obstruction, syphilis, combined system disease, injuries of the spinal cord, transverse myelitis and tumor of the spinal cord, we still have several cases not easily explained. In this article we present seven such cases for consideration.

In the absence of a well recognized cause of the paralysis, one must consider the various conditions existing in each case.

From the George F. Baker Clinic of the New England Deaconess Hospital, Dr. Elliott P. Joslin, Medical Director.

1. Jordan, W. R., and Watters, P.: Spontaneous Cerebral Vascular Accidents in Diabetes, Am. J. M. Sc. **186**:488 (Oct.) 1933. Jordan, W. R.: Epilepsy and Convulsions in Diabetes, Arch. Int. Med. **52**:664 (Nov.) 1933; Neurological Manifestations of Hypoglycemia, New England J. Med. **209**:715 (Oct. 12) 1933.

All the patients were middle-aged, their ages ranging from 42 to 60 years, with an average of 51.1 years. There were four women and three men. The duration of the diabetes varied from less than one year in case 5,494 to eleven and eight-tenths years in case 9,025, with an average of six and one-tenth years at the onset of symptoms in the bladder.[1a] The diabetes was mild in two cases, moderate in four and severe in one. The evidence indicates that a considerable period of inadequately controlled diabetes preceded the onset of the disturbance in the bladder in four cases, but not in the other three. All showed arteriosclerosis varying in degree from slight to advanced. There was no evidence that foci of infection exerted any influence on the disturbance in the bladder. Syphilis was not found in any case. Achlorhydria occurred in cases 8,404 and 3,645; in each the patient was at one time anemic. The use of alcohol as a cause of neuropathy seems remote, although two patients admitted its use to a slight degree. The spinal fluid was examined in five cases and showed no evidence of syphilis or of tumor of the spinal cord. In two specimens there was the slightest possible trace of globulin, a finding noted by Root and Rogers [2] in diabetic neuritis.

In the following brief histories we list neurologic observations.

REPORT OF CASES

CASE 1,443.—A man, 44 years old, who had diabetes for seven years, suffered from urinary retention (residual urine, 2,100 cc.). He complained of lancinating pains in the arms, chest and legs. Examination revealed pupils reacting less well to light than to distance, slight ataxia of the arms and legs and slight hypotonia. The knee jerks, which had been normal the year before, were absent, as were the ankle jerks. The Wassermann reactions of the blood and cerebrospinal fluid were negative. No written urologic record can be found, but the physician then in charge believes that cystoscopic examination was done and that it revealed no genito-urinary condition which might have caused the paralysis.

The patient died two and five-tenths years later of diabetes.

CASE 3,645.—A man, 60 years old, with diabetes of nine years' duration and advanced arteriosclerosis, began to suffer from nocturia, dribbling and incontinence at night. He also had shooting pains in the left thigh at night and complained of cold feet at night. During this period he had difficulty controlling the anal sphincter. Examination revealed slight mental confusion, pupils sluggish to light, a slightly sluggish right knee jerk, a very sluggish left knee jerk or absence of the jerk, absence of ankle jerks, decreased sensitivity over the lower portion of the right leg and foot and loss of tone of the anal sphincter. The Wassermann reactions of the blood and spinal fluid and the colloidal gold test were negative. The patient denied the use of alcohol. Urologic examination revealed residual urine (720 cc.) without prostatic or urethral obstruction. The bladder mucosa showed mild cystitis. Trabeculation was moderate. There was no diverticulum.

1a. It is possible that the initial symptoms in case 5,494 were due merely to glycosuria and that the real disturbance in the bladder began seven years later.

2. Root, H. F., and Rogers, M.: Diabetic Neuritis with Paralysis, New England J. Med. **202**:1049, 1930.

When the patient was first seen in September, he showed no evidence of anemia. The red blood cell count was 4,960,000, and the hemoglobin content was 91 per cent (Sahli). On January 27, following an attack of grip, he returned to the hospital. At this time there was definite, though not marked, hypochromic anemia. The total gastric acidity was 30 cc. of sodium hydroxide, but there was absence of lactic acid and free hydrochloric acid. The size of the red blood cells was below the average normal. During the next month pills of ferrous carbonate, 45 grains (2.7 Gm.) daily, were given, and during the second month in the hospital twelve intramuscular injections of liver extract were given. From then until May 15 three or four intramuscular injections of liver extract were given. The red blood cell count on March 20 was 3,650,000 (260,000 less than in January), but on May 15 the count was 5,660,000 and the hemoglobin content, 80 per cent. A diagnosis of secondary anemia was made, but the anemia may have been primary, the manifestations being precipitated and altered by infections. The retarded response to liver therapy may have been due to burns on the feet during the early part of the therapy. He survived amputation of a leg for gangrene in April 1934.

CASE 4,023.—A woman, 60 years old, with diabetes of three years' duration and moderate arteriosclerosis, complained of pain in the right leg on walking. Paresthesia disturbed her at night. Examination revealed a distended bladder (residual urine, 2,580 cc.). The pelvic and neurologic examinations gave negative results. The Wassermann reactions of the blood and spinal fluid were normal. Dr. James B. Ayer found no evidence of a nondiabetic lesion in the spinal cord. Cystoscopy revealed general redness of the bladder mucosa, with an abnormal amount of trabeculation.

The patient was in a satisfactory condition in April 1934, eight years after the onset, but she still required periodic catheterization and had residual urine at times as high as 2,730 cc.

CASE 5,494.—A man, 47 years old, noticed involuntary urination at night at the onset of diabetes. Five years later he began to have paresthesia of the legs and subsequently pains in the legs. Two years later the bladder was found to be distended (residual urine, 360 cc.). Examination revealed moderate arteriosclerosis, normal pupils and cranial nerves, sluggish knee and ankle jerks, weakness and atrophy and fibrillary twitchings of the muscles of the legs and, to a less degree, of the arms and variable sensitivity of the skin with areas of both hypo-esthesia and hyperesthesia. The Wassermann reaction of the blood was negative, and the spinal fluid was normal except for the slightest possible trace of globulin. No history of use of alcohol was obtained. Urologic examination revealed a slight irregularity of the prostate, but it was insufficient to cause obstruction. Trabeculation of the bladder was moderate.

He died seven months later of a gas bacillus infection following appendectomy.

CASE 6,360.—A woman, 55 years old, with diabetes of seven years' duration and mild arteriosclerosis, was found to have a distended bladder (residual urine, 900 cc.). She had no other neurologic symptoms. Examination revealed absence of the ankle jerks but no other neurologic signs. The Wassermann reaction of the blood was negative. There was no history of the use of alcohol. Cystoscopic examination revealed moderate chronic inflammation of the bladder. No cause other than neurologic disturbance was found.

The patient was alive more than six years after the onset of paralysis, although she had suffered amputation of a leg for gangrene and had a thyroidectomy. The

report of the last nurse indicates residual urine of 270 cc. In April 1934 a roentgenogram revealed a condition of the spine similar to that in two cases of spontaneous fracture recently reported by Root, White and Marble.[3]

CASE 8,404.—A woman, 42 years old, with diabetes of four and eight-tenths years' duration and slight arteriosclerosis, had diarrhea for six months and finally hematuria. Examination revealed no neurologic signs except sluggish knee jerks and absence of the ankle jerks. The bladder was distended (residual urine, from 360 to 900 cc.), and considerable gas was present. From rough tests the gas was thought to be air which presumably entered the bladder during catheterization. There was no history of the use of alcohol. No cause for the diarrhea was found except achlorhydria and a weak anal sphincter. The Wassermann reaction of the blood was negative, as was the spinal fluid except for the slightest possible trace of globulin. Cystoscopic examination revealed marked chronic cystitis with a number of hemorrhagic spots in the wall of the bladder. No tumor or diverticulum was present. The appearance was consistent with a neurologic cause. Roentgenograms of the urinary tract showed no abnormality other than air in the bladder.

Gastric analysis revealed an absence of free hydrochloric acid. Two years previously the red blood cells numbered 3,350,000, and liver therapy was recommended. At the time of our examination she was not anemic, but the possibility of pernicious anemia was considered. She died four months later of pneumonia.

CASE 9,025.—A woman, 50 years old, with mild diabetes of eleven and eight-tenths years' duration, a blood pressure of 200 systolic and 120 diastolic and moderate arteriosclerosis, entered the hospital because of urinary retention and uremia. At first the retention was thought to be due solely to a urethral stricture, but correction of this defect, while causing some amelioration of the symptoms, did not abolish the retention, which seemed to be due to paralysis of the wall of the bladder. There were no neuritic symptoms. Examination revealed normal pupils. The knee reflexes were present. The Wassermann reaction of the blood was negative. Cystoscopic examination was not done at first for fear of hemorrhage if the bladder was emptied. Later the amount of residual urine varied from 90 to 300 cc. For the last three years the urethra has maintained a normal caliber of a no. 22 French catheter, yet the residual urine has persisted, and the nonprotein nitrogen content of the blood has varied from 44 to 62 mg. since June 1932.

She was living in March 1934, nearly four years after the onset.

COMMENT

Study of these cases reveals no definite cause of the paralysis. In six the symptoms in the bladder accompanied paresthesia and changes in the reflexes attributable to neuritis of diabetic origin. Two patients had achlorhydria and at one time had anemia, though not definitely of the pernicious type. Arteriosclerosis and diabetes were the only diseases present in all cases. The former may give rise to paralysis, and we believe that it was a factor in these cases. The relationship between arteriosclerosis and diabetic neuropathy was described recently by Woltman and Wilder.[4] The influence of diabetes on paralysis of the bladder

3. Root, H. F.; White, P., and Marble, A.: Abnormalities of Calcium Deposition in Diabetes Mellitus, Arch. Int. Med. **53**:46 (Jan.) 1934.

4. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929.

may be judged in part by its influence on the nerve tissue elsewhere in the body. That diabetes is often associated with neuropathy is well known. Such neuropathy is frequently designated neuritis and in some cases as diabetic tabes. Granting that neuritis was present in these cases, are we justified in suspecting it of causing the vesical paralysis?

PARALYSIS OF THE BLADDER AND NEURITIS

Involvement of the bladder in neuritis of any etiology appears to be rare. Yet many authors have reported evidence of involvement of the spinal cord in various forms of neuritis, and Campbell [5] stated that "in posterior tract disease, bladder disturbances are likely to be the rule." Feiling [6] stated that the central as well as the peripheral nervous system is damaged in many cases of neuritis. Hyslop and Kraus [7] reviewed the literature on lead paralysis and concluded that the neuritis involves the cord as well as other parts of the nervous system. Eijkman [8] found changes in the spinal cord in experimental beriberi; and Voegthin and Lake [9] reported changes in the spinal cord in a similar deficiency neuritis in a large proportion of their animals. Boxwell [10] reported vesical involvement in alcoholic neuritis, Campbell [5] in alcoholic, lead and toxic neuritis and Caulk and Greditzer [11] in lead poisoning. Holmes [12] found involvement of the sphincters in cases of polyneuritis of the type with facial diplegia, and Harris [13] said that paralysis of the sphincter is occasionally seen in neuritis. Kennedy [14] mentioned paralysis of the sphincter in diphtheritic neuritis.

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5. Campbell, M. F.: Bladder Disturbances of Nerve Lesion Origin, M. J. & Rec. (supp.) **119**:40 (March 5) 1924.

6. Feiling, A.: Multiple Neuritis, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 6, p. 647; quoted by Hyslop and Kraus.[7]

7. Hyslop, G. H., and Kraus, W. M.: Pathology of Motor Paralysis by Lead, Arch. Neurol. & Psychiat. **10**:444 (Oct.) 1923.

8. Eijkman, C.: Eine Beri-Beri-ähnliche Krankheit der Hühner, Virchows Arch. f. path. Anat. **148**:523, 1897.

9. Voegthin, C., and Lake, G. C.: Experimental Mammalian Polyneuritis Produced by a Deficient Diet, Am. J. Physiol. **47**:558, 1919.

10. Boxwell: Disordered Bladder Function in Nervous Diseases, Tr. Roy. Acad. Med. Ireland **32**:63, 1914.

11. Caulk, J. R., and Greditzer, H. G.: Bladder in Diseases of Central Nervous System, Am. J. Syph. **1**:42, 1917; Interstate M. J. **23**:36, 1916.

12. Holmes, G.: Brit. M. J. **2**:37, 1917; quoted by Wilson, G., and Robertson, H. F.: Facial Diplegia in Polyneuritis, Am. J. M. Sc. **183**:680, 1932.

13. Harris, W.: Multiple Peripheral Neuritis, Proc. Roy. Soc. Med. (Sect. Neurol.) **16**:13, 1923.

14. Kennedy, F.: Focal Infections Implicating the Nervous System, Am. J. M. Sc. **185**:305, 1933.

DISTURBANCES IN THE BLADDER IN DIABETES DUE TO INVOLVEMENT OF THE SPINAL CORD

Reports dealing with vesical paralysis in persons with diabetes are rare. Marchal de Calvi [15] quoted LeBret as reporting a diabetic patient with a slight disturbance in the bladder, but he did not disclose the nature of the change. Bonardi [16] reported a diabetic patient with loss of sphincter control. Root [17] mentioned two diabetic patients with concomitant pernicious anemia in whom there developed paralysis of the bladder. Von Noorden and Isaac [18] referred to urinary urgency, especially at night, not apparently due to the polyuria in persons with diabetes. Joslin [19] reported cases of diabetes of this series (cases 1,443 and 5,494) as illustrations of pseudotabes, but did not mention the symptoms in the bladder. McKittrick and Root [20] added a third case. On the other hand, Caulk and Greditzer [11] reported one hundred and seventeen cases of disturbance in the bladder due to involvement of the spinal cord without mentioning diabetes as a cause in any case. Williamson [21] and Smith [22] denied that changes in the sphincter are caused by diabetes. Yet clinical or pathologic evidence of involvement of the spinal cord in diabetic patients has often been reported.[23] One form

15. Marchal de Calvi: Recherches sur les accidents diabétiques, Paris, P. Asselin, 1864.

16. Bonardi, E.: Sclerosi diffusa pseudo-sistematizzata della midolla spinale con polinevrite in un caso di diabete mellito, Morgagni **39**:557, 1897.

17. Root, H. F.: New Cases of Diabetes and Pernicious Anemia, New England J. Med. **208**:819, 1933.

18. von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, Berlin, Julius Springer, 1927.

19. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 734.

20. McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928, p. 253.

21. Williamson, R. T.: Symptoms Due to Peripheral Neuritis or Spinal Cord Lesions in Diabetes Mellitus, Rev. Neurol. & Psychiat. **5**:550, 1907.

22. Smith, W. A.: Diabetic Neuritis, South. M. J. **19**:773, 1926.

23. Pryce, T. D.: Perforating Ulcers of Both Feet Associated with Diabetes and Ataxic Symptoms, Lancet **2**:11, 1887. Pavy: On Diabetes, M. News **51**: 357 (Sept. 24) 1887; quoted by Pryce.[22] Leyden, E.: Die Entzündung der peripheren Nerven, Deutsche mil.-ärztl. Ztschr. **17**:49 and 100, 1888; quoted by Althaus. Althaus, J.: Neuritis of the Circumflex Nerve in Diabetes, Lancet **1**:455, 1890. Minor, L.: Etude de l'étiologie du tabes, Arch. de neurol. **17**:362, 1889. Sandmeyer, W.: Beitrag zur pathologischen Anatomie des Diabetes mellitus, Deutsches Arch. f. klin. Med. **50**:381, 1892. Leichtentritt, H.: Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893, p. 32; quoted by Woltman and Wilder.[4] Leyden: Beiträge zur Klinik des Diabetes mellitus, Wien. med. Wchnschr. **43**:926, 1893. Williamson, R. T.: Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus, Brit. M. J. **1**:398, 1894; Changes in the Spinal Cord in Diabetes Mellitus, ibid.

of diabetic neuritis is even spoken of as pseudotabetic.[24] Nicolesco and Raïleanu [25] noted that the extrapyramidal and central vegetative systems were particularly damaged in diabetes. In this clinic we have noted Argyll Robertson pupils, ataxia and loss of sense of position of the big toe, apparently due to diabetes. Furthermore, diabetes is a disease of elderly people, and it is usually associated with considerable arteriosclerosis which also causes involvement of the spinal cord (Woltman,[26] Price [27]). This evidence of potential involvement of the bladder in diabetes gives ground for suspecting diabetic neuropathy as a cause of the paralysis.

In spite of eliminating cases of combined system disease, we are confronted with the possibility of this disease as a cause, since a study of the history in one case and of the subsequent course in another disclosed anemia. All seven in the series may represent cases of combined system disease with latent anemia, but the available data (absence of anemia in five cases and dissimilarity between the changes in the nerves and those usually found in combined system disease) do not make this supposition reasonable.

The mechanism of the production of the paralysis is not known. Elliott [28] showed the tonic action of the central nervous system on the bladder, and we have mentioned many authors who found lesions of the spinal cord, frequently in the posterior tract, in diabetic patients. Pre-

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1:122, 1904. Nonne, M.: Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lähmung bei Diabetes mellitus, Berl. klin. Wchnschr. **33**:207, 1896. Souques, A., and Marinesco, G.: Lésions de la moelle épinière dans un cas de diabète sucré, Rev. neurol. **5**:242, 1897. Marinesco, G.: Cas de paraplégie diabétique, ibid. **9**:719, 1901. Ossokine, N.: Contribution à l'étude de l'anatomie pathologique de la moelle dans le diabète sucré, Kazanskiy med. j. **1**:370, 1901; abstr., ibid. **10**:993, 1902. Schweiger, L.: Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes, Wien. med. Wchnschr. **57**:1549, 1907. Bonardi.[16] Woltman and Wilder.[4]

24. Major, R. H.: Tabes Diabetica, J. A. M. A. **83**:2004 (Dec. 20) 1924. Wakefield, E. G.: Diabetic Neuritis, Proc. Staff Meet., Mayo Clin. **3**:256, 1928. Angle, F. E.: Tabes Diabetica, U. S. Nav. M. Bull. **26**:81, 1928. (The patient with pseudotabetic diabetes whose case was reported by Angle had symptoms in the bladder, but he also had an enlarged prostate and uncontrolled diabetes, which may give rise to severe symptoms, which are probably brought about by local prostatic irritation and disappear when the diabetes is regulated. The cases we report here are not of this type.)

25. Nicolesco, I., and Raïleanu, D.: Altérations du système nerveux central dans deux cas de diabète sucré, Compt. rend. Soc. de biol. **95**:122, 1926.

26. Woltman, H. W.: Arteriosclerosis of the Nervous System, M. Clin. North America **5**:511, 1921.

27. Price, G. E.: Arteriosclerosis of the Nervous System, M. J. & Rec. **118**: 425, 1923.

28. Elliott, T. R.: Innervation of the Bladder and Urethra, J. Physiol. **35**: 367, 1907.

sumably, diabetes affects the nerves to the bladder as it does those to the legs, either directly or indirectly through the lesions of the spinal cord. Woltman and Wilder [4] described these lesions and summed up the literature on the subject.

TREATMENT

The objectives are: to maintain proper control of the diabetes; to administer a properly balanced diet containing an abundance of vitamins and to keep the patient in as good general condition as possible. The local treatment is directed against urinary retention and infection. Prolonged constant drainage has been helpful. Periodic catheterization has been the rule. Various authors [29] have described forms of treatment for the bladder affected by changes in the spinal cord. Cahill [29d] and Priestley [30] recommended systematic pressure on the bladder to stimulate the automatic emptying noted by Elliott [28] and Osgood.[31] We have used this method in only one case (case 4,032) and without success, although it would seem especially adaptable to diabetic patients, since we have not infrequently noted a return of the reflexes in patients with diabetic neuritis and almost all patients with paralysis of skeletal muscles eventually regain control of the muscles. Resection of the presacral (sympathetic) nerve, as practiced in some cases by Learmouth,[29f] has not been tried, because in diabetes there is a more or less generalized involvement of the nervous system and not a sharp localization to one set of nerves such as the parasympathetic system. Goldberg,[32] in discussing retention due to urethral stricture, recommended that diabetic patients with marked strangury, especially at night, be catheterized, so that retention of urine, curable in the beginning, will not be overlooked. In our case 9,025, with urethral stricture, we were unable to avoid the subsequent retention, even though catheterization and dilation of the stricture were repeatedly done. The subsequent retention seemed due to paralysis of the wall of the bladder, but it may have

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29. (*a*) Smith, G.: Bladder Disturbance Due to Nerve Lesions, J. A. M. A. **69**:1323 (Oct. 20) 1917. (*b*) Burns, J. E.: Bladder Changes Due to Lesions of the Central Nervous System, Surg., Gynec. & Obst. **24**:659, 1917. (*c*) Corbus, B. C., and O'Conor, V. J.: The Tabetic Bladder from the Standpoint of the Urologist, J. A. M. A. **79**:1750 (Nov. 28) 1922. (*d*) Cahill, G. F.: Treatment of Bladder Paralysis Due to Nontabetic Spinal Cord Lesions, Am. J. Surg. **5**:442, 1928. (*e*) Boyd, M. L., and Bailey, M. K.: Suprapubic Cystotomy in Bladder Paralysis, J. Urol. **21**:623, 1929. (*f*) Learmouth, J. R.: Neurosurgery in Treatment of Diseases of Urinary Bladder, J. Urol. **26**:229, 1931. (*g*) Caulk and Greditzer.[11] Campbell.[5]

30. Priestley, J. T.: Spinal Cord Bladder, J. Urol. **21**:635, 1929.

31. Osgood, A. T.: Significance of Disturbances of the Function of the Bladder, Bull. New York Acad. Med. **2**:194, 1926.

32. Goldberg: Retention of Urine Due to Complications of Urethral Stricture, Ztschr. f. Urol. **19**:359, 1925.

been contributed to by the previous stricture. We believe that diabetic patients are particularly susceptible to neuritis and that a factor insufficient to produce neuritis in a person who has no diabetes may cause it in a person with diabetes.

SUMMARY AND CONCLUSIONS

1. Seven cases of diabetes with urinary retention are reported.

2. The nature of the disturbance in the bladder, the absence of any other known cause and in many cases the close association with diabetic neuritis suggest that the changes in the bladder are due to such neuropathy.

3. The treatment consists of treatment of the diabetes and of any associated neuritis, the prevention or treatment of urinary infection and catheterization at intervals to prevent uremia.

4. The prognosis is not good. Three of the seven patients are dead. None of our patients has regained the power to empty the bladder completely. The blood nitrogen, on the other hand, has not risen to a serious level, and the general health of the patients has remained reasonably good.

NEUROPATHY IN DIABETES MELLITUS

LIPID CONSTITUENTS OF THE NERVES CORRELATED WITH THE CLINICAL DATA

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The frequent occurrence of neurologic symptoms and signs is one of the striking features noted in a clinic for the treatment of diabetes. Although the frequency of individual symptoms and signs varies, it is safe to say that about 50 per cent of diabetic patients show evidence of a disturbed nervous system. In 1884, Bouchard [1] noted absence of knee jerks in 28.8 per cent of diabetic patients, and in 1931 Sevringhaus [2] recorded pain in 49 per cent and reduced reflexes in 57.3 per cent of diabetic patients specially examined for these changes. Among 461 of our diabetic patients in whom the patellar and achilles reflexes were tested, we found decreased or absent reflexes in 45.3 per cent.

Diabetic neuritis is not a new condition, yet little progress seems to have been made in its prevention or cure. Although previous to 1864 symptoms suggestive of the degeneration of nerves in diabetic persons had been reported, it was in that year that Marchal de Calvi [3] introduced the conception that such lesions may well be a result of diabetes. Following the publication of Bouchard's paper, many contributions to the subject were made, and in 1890 Auché [4] summed up the pertinent work, giving a fairly complete picture of diabetic neuritis. Since then numer-

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1. Bouchard: Sur la perte des reflexes tendineux dans le diabète sucré, Progrès med. **12**:819, 1884.

2. Sevringhaus, E. L.: Study of Five Hundred Diabetics, Am. J. M. Sc. **182**:311, 1931.

3. Marchal de Calvi: Recherches sur les accidents diabétiques, Paris, P. Asselin, 1864.

4. Auché, B.: Des altérations des nerfs périphériques chez les diabétiques, Arch. de méd. exper. et d'anat. path. **2**:635, 1890.

ous papers have been published. Williamson [5] wrote profusely on the subject, and he and many others [6] described pathologic changes associ-

5. Williamson, R. T.: Changes in the Posterior Column of the Spinal Cord in Diabetes Mellitus, Brit. M. J. **1**:398, 1894; On the Knee-Jerks in Diabetes Mellitus, Lancet **2**:138, 1897; Note on the Tendo-Achilles Jerk and Other Reflexes in Diabetes Mellitus, Rev. Neurol. & Psychiat. **1**:667, 1903; Changes in the Spinal Cord in Diabetes Mellitus, Brit. M. J. **1**:122, 1904; Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus, Rev. Neurol. & Psychiat. **5**:550, 1907; Diabetic Neuritis, Practitioner **112**:85 (Feb.) 1924.

6. (*a*) Minor, L.: Etude de l'étiologie du tabes, Arch. de neurol. **17**:362, 1889. (*b*) Pryce, T. D.: Perforating Ulcers of Both Feet Associated with Diabetes and Ataxic Symptoms, Lancet **2**:11, 1887; (*c*) Diabetic Neuritis with a Clinical and Pathological Description of Three Cases of Diabetic Pseudotabes, Brain **16**:416, 1893. (*d*) Eichhorst, H.: Neuritis diabetica und ihre Beziehungen zum fehlenden Patellarsehnenreflex, Virchows Arch. f. path. Anat. **127**:1, 1892. (*e*) Sandmeyer, W.: Beitrag zur pathologischen Anatomie des Diabetes mellitus, Deutsches Arch. f. klin. Med. **50**:381, 1892. (*f*) Leyden: Beiträge zur Klinik des Diabetes mellitus, Wien. med. Wchnschr. **43**:926, 1893. (*g*) Leichtentritt, H.: Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893, p. 32; quoted by Woltman and Wilder.[6x] (*h*) Fraser, T. R., and Bruce, A.: Case of Diabetic Neuritis, Edinburgh M. J. **42**:300, 1896; Multiple Diabetic Neuritis, Brit. M. J. **1**:1149, 1895. (*i*) Nonne, M.: Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lähmung bei Diabetes mellitus, Berl. klin. Wchnschr. **10**:207, 1896. (*j*) Fleming, R. A.: Two Cases of Peripheral Neuritis, Brain **20**:56, 1897. (*k*) Souques, A., and Marinesco, G.: Lésions de la moelle épinière dans un cas de diabète sucre, Rev. neurol. **5**:242, 1897. (*l*) Bonardi, E.: Sclerosi diffusa pseudo-sistematizzata della midolla spinale con polinevrite in un caso di diabete mellito, Morgagni **39**:557, 1897. (*m*) Leyden and Goldscheider: Die Erkrankungen des Rückenmarks und der Medulla oblongata, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Holder, 1900, vol. 10, p. 500; quoted by Woltman and Wilder.[6x] (*n*) Naunyn, B.: Der Diabetes mellitus, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, A. Holder, 1900, vol. 7, p. 251; quoted by Woltman and Wilder.[6x] (*o*) Findlay, J. W.: Changes in the Peripheral Nerves in a Case of Diabetes Mellitus, Tr. Med.-Chir. Soc. Glasgow **3**:441, 1902. (*p*) Ossokine, N.: Contribution à l'étude de l'anatomie pathologique de la moëlle dans le diabète sucre, Rev. neurol. **10**:993, 1902. (*q*) Marinesco, G.: Cas de paraplégie diabétique, ibid. **9**:719, 1901. (*r*) Wittmaack, K.: Degenerative Neuritie bei Diabetes mellitus, Ztschr. f. Ohrenh. **53**:19, 1907. (*s*) Schweiger, L.: Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes, Wien. med. Wchnschr. **57**:1549, 1907. (*t*) Bramwell, B.: Diabetes: Marked Changes in the Posterior Tibial and Plantar Nerves, Clin. Studies **5**:279, 1907. (*u*) Nicolesco, I., and Raïleanu, D.: Altérations du système nerveux central dans deux cas de diabète sucré, Compt. rend. Soc. de biol. **95**:122, 1926; (*v*) Lésions du système nerveux central dans le diabète sucré, Rev. neurol. **1**:31, 1927. (*w*) Wohl, M. G.: Avitaminosis in the Course of Diabetes, J. A. M. A. **87**:901 (Sept. 18) 1926. (*x*) Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929. (*y*) Root, H. F., and Rogers, M. H.: Diabetic Neuritis with Paralysis, New England J. Med. **202**:1049, 1930. (*z*) Auché.[4]

ated with diabetic neuritis. Lesions have been described in the brain, spinal cord, posterior nerve roots and peripheral nerves. Auché [4] believed that the nerve lesions could not be explained by changes in the spinal cord, because normal nerve tissue was found proximal to a diseased portion and the peripheral part of the nerve showed greater pathologic change than the proximal portion. Woltman and Wilder [6x] subscribed to this view. One notes in the description of changes in the nerves the marked degeneration of myelin, which is not, however, peculiar to diabetes.

There are numerous suggestions that this degeneration of diabetic nerves may be of metabolic origin. Raven [7] noted the return of the knee jerks in a diabetic patient who simultaneously regained health and strength. Althaus [8] reported an increase in the nervous condition when the diabetic diet was limited too much, and he believed cachexia to be a cause of the neuritis. Pryce [6c] also suggested prolonged malnutrition as a cause, whereas Harris,[9] while excluding hyperglycemia and acetone bodies as causes, suggested that the cause was a neurotoxin of the autotoxemic deficiency type. Nicolesco and Raïleanu [6v] also held to the theory of prolonged intoxication due to metabolites. Angle [10] reported an interesting case of diabetic tabes which developed while the urine was sugar-free, improving markedly when a diet moderately high in carbohydrate was substituted for the previous diet high in fat. Woltman and Wilder [6x] also noted improvement in the reflex activity when emaciated diabetic patients became properly nourished. The isolated reports of disease caused by dietary deficiency in diabetic patients, for instance, those of Wohl [6w] and Bitzer,[11] bring up the possibility of some similar condition as the cause of the changes in the nerves. Possibly on account of the well known deficiency diseases, such as combined system disease and beriberi, one notices a trend toward the belief that various forms of neuritis may be due to some dietary deficiency (Wechsler [12]). Why the myelin so often bears the brunt of the attack is unknown. The observation of Moore, Brodie and Hope [13] that in

7. Raven, T. F.: Disappearance and Return of Knee-Jerks in Diabetes, Brit. M. J. **1**:303, 1887.

8. Althaus, J.: Neuritis of the Circumflex Nerve in Diabetes, Lancet **1**: 455, 1890.

9. Harris, W.: Toxic Polyneuritis, Brain **45**:415, 1922; Multiple Peripheral Neuritis, Lancet **2**:849, 1922; Multiple Peripheral Neuritis, Proc. Roy. Soc. Med. (Sect. Neurol) **16**:13, 1923.

10. Angle, F. E.: Tabes Diabetica, U. S. Nav. M. Bull. **26**:81, 1928.

11. Bitzer, E. W.: A Case of Beri-Beri in a Diabetic, J. Florida M. A. **17**: 577, 1931.

12. Wechsler, I. S.: Unrecognized Cases of Deficiency Polyneuritis, M. J. & Rec. **131**:441, 1930.

13. Moore, C. U.; Brodie, J. L., and Hope, R. B.: Some Effects of Inadequate Maternal Diets, Am. J. Physiol. **82**:350, 1927.

their experiments on the neuritis secondary to vitamin B deficiency the clinical manifestations of neuritis appeared in the young rats "only when the myelin normally should be fully laid down" is interesting and may explain why diabetic children suffer so little from neuritis. The work of Brickner,[14] Cherry and Crandall,[15] and Weil and Crandall [16] suggests the possibility of some lipolytic enzyme as an etiologic agent. The common observation in clinics for the treatment of diabetes that degeneration of nerves occurs far more often in the elderly person with a mild case of diabetes than in the young person with a severe case is better evidence than the experiments of Auché [4] and Eichhorst [6d] that diabetic neuritis is not a result of hyperglycemia only. One must look for a more subtle cause. Many observations incline one to admit that vascular disease is a more important factor. Pryce,[6c] Rimbaud [17] and recently Woltman and Wilder [6x] have all been struck by this feature and many authors [18] have discussed the relationship of arteriosclerosis to neuritis in persons not having diabetes. The arteriosclerosis in persons with diabetes has often been attributed to faulty fat metabolism, and it is not impossible that the degenerative changes in the nerves may be due as much to defective metabolism as to the vascular disease associated with it. Considering the definite disorder of fat metabolism in diabetes and the abnormality of the lipid myelin sheath in this disease, we wondered about the fatty substances present in the nerves of diabetic persons and the changes wrought by the diabetes.

From the earliest work on degenerative diseases of the nervous system chemical evidence of the breakdown of nervous tissue was obtained by discovery of certain products of disintegration in the cerebrospinal fluid and in the blood. The determination of phosphorus

14. Brickner, R. M.: New York State J. Med. **31**:885 (July 15) 1931; quoted by Weil and Crandall.[16]

15. Cherry, I. S., and Crandall, L. A.: Specificity of Pancreatic Lipase, Am. J. Physiol. **100**:266, 1932.

16. Weil A., and Crandall, A. L.: Relationship Between Lipase and Neurotoxic Action of Dog's Serum After Experimental Liver Damage, Proc. Soc. Exper. Biol. & Med. **29**:388, 1932.

17. Rimbaud, L.: Un cas de nevrité diabétique, Gaz. d. hôp. **82**:1555, 1909.

18. Schlesinger, H.: Ueber eine durch Gefässerkrankungen bedingte Form der Neuritis, Neurol. Centralbl. **14**:578, 1895. Franceschi, F.: Polinevrite ed arteriosclerosi del sistema nervoso centrale e periferico, Riv. di pat. nerv. **8**:193, 1903. Woltman, H. W.: Arteriosclerosis of the Nervous System, M. Clin. North America **5**:511, 1921. Price, G. E.: Arteriosclerosis of the Nervous System, M. J. & Rec. **118**:425, 1923. Alpers, B. J., and Wolman, I. J.: Arteriosclerotic Disease of the Optic Nerve, Arch. Ophth. **6**:21 (July) 1931. Priestley, J. B.: Histopathology of Peripheral Nerves Removed from Extremities Amputated for Arteriosclerotic Gangrene, Proc. Staff Meet., Mayo Clin. **6**:517, 1931.

constitutes one of the earliest attempts to study changes under pathologic conditions. Halliburton [19] studied phospholipid degeneration in nerve tissue and supported the theory that the phosphorus portion of the molecules was liberated, leaving behind the fatty portion of the compound. The phosphorus content decreased in the tissues and increased in the blood, and the nitrogen level increased in the blood of experimental animals in which the nerve had been cut and allowed to degenerate.

A few studies have been made comparing the chemical content of normal brains and brains in which a pathologic change has occurred. In dementia praecox, Koch [20] and Koch and Mann [21] found that neutral sulphur was diminished while inorganic sulphur was increased. The phosphorus content did not show a notable change, either as a whole or distributed.

Smith and Mair [22] found in hemiplegic softening of the brain that the cholesterol content was increased, the excess appearing in the form of esters, while the level of cerebrosides and lipid phosphorus was reduced. In dementia paralytica these authors noted that the cholesterol level was normal, while the cerebroside content was reduced 50 per cent and the lipid phosphorus balance was reduced, but to a less extent.

In progressive paralysis Carbone and Pighini,[23] Pighini [24] and Pighini and Barbieri [25] stated that there was an increase in water, protein and cholesterol and a decrease in saturated and unsaturated phospholipids and cerebrosides. They observed an increase in lipid granules when the metabolism of the cell was changed in some way, as in senescence, in poisoning or in certain diseases of the nervous system. The chemical picture of paralysis is similar to that of lipid degeneration.

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19. Halliburton, W. D.: Die Biochemie der peripheren Nerven, Ergebn. d. Physiol. **4**:23, 1905.

20. Koch, W.: Zur Kenntnis der Schwefelverbindungen des Nervensystems, Ztschr. f. physiol. Chem. **53**:496, 1907.

21. Koch, W., and Mann, S. A.: A Chemical Study of the Brain in Healthy and Diseased Conditions, with Special Reference to Dementia Praecox, Arch. Neurol. & Psychiat. **4**:174, 1909.

22. Smith, J. L., and Mair, W.: On a Method of Quantitative Analysis of Tissue Lipoids, with a Preliminary Note on Degeneration in the Brain, J. Path. & Bact. **16**:131, 1911.

23. Carbone, D., and Pighini, G.: Beitrag zur chemischen Zusammensetzung des Gehirns bei der progressiven Paralyse, Biochem. Ztschr. **46**:450, 1912.

24. Pighini, G.: Beitrag zur chemischen Zusammensetzung des Gehirns bei der progressiven Paralyse, Biochem. Ztschr. **63**:304, 1914.

25. Pighini, G., and Barbieri, P.: Chemische und histochemische Untersuchungen über die lipoiden Abbaustoffe des Gehirns bei der progressiven Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **25**:353, 1914.

Koch [26] found in the brain of a patient with dementia paralytica a slight increase in the water content in the fresh tissue, a relative increase in the protein and possibly also the cholesterol content and a decrease of lipids as a whole. Of the lipids, the unsaturated phospholipids showed the most consistent decrease, while the saturated cerebrosides and sulphatides showed less consistent decreases. He found marked increases in extractives (water-soluble substances). The lipid nitrogen and lipid phosphorus levels were decreased, while the extractive phosphorus and nitrogen values were increased. He suggested that the less stable unsaturated phospholipids break down from their physical or physicochemical combination with proteins and other lipids, with the subsequent appearance of the split products in the extractive fraction.

Singer [27] studied the brains of five persons with progressive paralysis and found the petroleum ether extracts increased per gram of substance. The nitrogen content, expressed in per cent of dry substance, diminished. The choline nitrogen fraction, corresponding to the lecithin, was reduced to one third of normal, and in some cases there was a reduction in aminonitrogen also. Galactoside nitrogen could be demonstrated only in traces. The total choline-nitrogen ration changed from the normal value of 1.4 : 1 to 3.1 : 1. He thought that the diminution of lecithin should be considered a symptom of marasmus in general rather than a specific symptom of paralysis, since it is found in cachectic persons.

Koch and Riddle [28] studied the brains of normal and ataxic pigeons and noted in the latter an increase in the content of water, protein, protein phosphorus and water-soluble phosphorus, while there was a decrease in values for lipids, cholesterol, phospholipid, sulphatide and total phosphorus.

May [29] showed that an experimental traumatic lesion of a cerebral hemisphere of the guinea-pig gives rise to an increase in the water, nitrogen and sulphur content and to a decrease in the phosphorus content of the disintegrating cerebral matter. In the degenerating peripheral

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26. Koch, M. L.: Chemical Investigations of the Central Nervous System under Normal and Pathologic Conditions: Chemical Examination of the Central Nervous System in Two Cases of General Paralysis, Arch. Neurol. & Psychiat. **7**:488, 1922.

27. Singer, K.: Studies on the Physiologic and Pathologic Chemistry of the Brain: III. The Phosphatides of the Petroleum Ether Fraction of the Brain in Progressive Paralysis and Marasmus, Biochem. Ztschr. **198**:340, 1928.

28. Koch, M. L., and Riddle, O.: The Chemical Composition of the Brain of Normal and Ataxic Pigeons, J. Comp. Neurol. **31**:83, 1919.

29. May, R. M.: Etudes microchimiques sur le système nerveux: II. L'eau, l'azote, le soufre et le phosphore cérébraux au cours de l'encéphalite traumatique expérimentale du Cobaye, Bull. Soc. chim. biol. **11**:312, 1929.

nerves of the rabbit, May [30] found that the water content increased to 14 per cent above normal during the first month and then fell back to normal. The total phosphorus level diminished progressively to a third of the normal value during the first two months. The lipid phosphorus decreased to a tenth of the normal in one hundred days when histologic examination revealed complete reabsorption of the lipid products of the nerve. The protein phosphorus content, after an initial rise, fell to a third of the normal. A phosphorus fraction, the composition of which was unknown but which was soluble in alcohol and insoluble in a mixture of ether, benzene and water, fell to a third of the normal. The water-soluble phosphorus fraction increased to 25 per cent above normal during the first few days and to 35 per cent during six months. May suggested that the complex cellular constituents (phospholipids and nucleproteins) disintegrate to form water-soluble phosphorus compounds. Degeneration of the nerve brings back the water-soluble form in which phosphorus enters the organism. There is also the possibility that the increase of water-soluble phosphorus may represent incomplete synthesis in degenerate nerves.

Degeneration of nerves seems therefore to be characterized by definite changes in the chemical composition. The content of water and protein is increased. Cholesterol is increased or remains the same. There may be an increase in cholesterol esters. Total lipids are decreased, the phospholipids to a greater extent than the cerebrosides. Water-soluble phosphorus compounds are increased.

We have undertaken this study in the hope of throwing some light on the important subject of diabetic neuritis. The cases studied were in patients of Dr. Elliott P. Joslin and his associates. The clinical features from a large series of cases are to be described in a separate paper. Here we merely present the results obtained in the specimens of nerves already examined chemically and try to correlate them with the clinical findings in the cases studied. The twenty specimens of nerves were obtained from eighteen diabetic patients at autopsy or after the amputation of a leg. In cases of amputation the posterior tibial nerve was selected, and at autopsy the femoral or sciatic nerve near the point of exit from the vertebral column was used. Naturally in such a small series of patients we lack certain types, especially the young person with severe diabetes.

The patients were of the arteriosclerotic type with relatively mild diabetes, the type in whom one often finds neuropathy. The ages ranged from 52 years in case 9,827 to 79.8 years in case 10,803, with

30. May, R. M.: Etudes microchimiques sur le système nerveux: III. L'eau et les combinations phosphorées du nerf au cours de la dégénérescence, Bull. Soc. chim. biol. **12**:934, 1930.

an average of 66.4 years. Arteriosclerosis was present in all cases, although in case 9,827, the sclerosis was rather slight. Thirteen of the twenty nerves were taken from patients with advanced arteriosclerosis. There was deficient circulation in the legs in seventeen patients, but four had only a slight deficiency. The duration of the diabetes varied from eight-tenths year in case 11,082 to twenty-four years in case 10,964, with an average for the eighteen cases of seven and eight-tenths years. Only one patient had diabetes for less than one year, and seven had it for ten years or more. The diabetes was mild in fifteen cases and of moderate severity in three. There was no case of severe diabetes, but it is to be remarked that for several days preceding death, one patient (case 9,827), in spite of a heavy dosage of insulin, had considerable hyperglycemia due to septicemia with cavernous sinus thrombosis, although prior to the infection the diabetes had been mild and well controlled. In the sixteen cases in which we know something of the control of the diabetes prior to the condition causing admission to the hospital only three patients had poorly controlled diabetes, and in twelve the diabetes had apparently been well regulated. Unfortunately the cholesterol content was determined only in cases 3,575 and 10,964, in which the respective values were 150 and 208 mg. per hundred cubic centimeters, both being within normal limits. Nor do we know the gastric acidity in all cases. The three patients tested (cases 2,629, 3,575 and 10,964) showed free hydrochloric acid. There was a history of the use of alcohol for only one patient (case 11,128) of the eleven questioned about this, and five of the other seven patients were women. A focus of infection other than the infection for which the patient entered the hospital was present in only one (case 3,575) of the fifteen examined for this condition. There was no evidence of syphilis in any case, but one patient (case 10,804) died shortly after admission and a Wassermann test was not done. Thirteen of the eighteen patients had amputations performed; in eight gangrene and in five infection was the cause of amputation. Five cases were fatal, two patients dying of infection, one of intestinal obstruction, one of coronary thrombosis and one of a combination of gangrene, infection and nephritis. Only two of the eighteen patients complained of neuritic symptoms, but it must be remembered that they were quite ill and that the existing illness probably obscured many minor symptoms. In case 10,804 there was complaint of pain in the legs and in case 11,106 of cramps in the legs. Owing to the nature of the lesions of the extremities or to the emergency of the condition a neurologic examination was rarely made. However, the knee jerks, tested in sixteen patients, were normal in only eight. The ankle jerks were normal in only two of the twelve patients tested. All other patients tested showed hypo-activity of the

tendon reflexes. Sensation to pinprick was normal in three of the six patients so examined. The pupillary reaction was sluggish in case 11,080, and there were fixed pupils in case 11,108.

The clinical symptoms and signs in such cases under ordinary conditions will be discussed in another paper, as yet unpublished. In that article we shall describe two groups of diabetic patients similar to those studied here. One of the groups includes patients having certain neurologic changes associated with defective circulation in the legs; the second group includes those showing some evidence of chronic degenerative changes in the nerves, such as sluggish tendon jerks, paresthesia and mild pain in the legs associated with arteriosclerosis and diabetes. In the former group the average age was 58.1 years; in the latter, 59.2. The average duration of the diabetes was, respectively, five and four-tenths years and four and five-tenths years at the onset of the neuritic symptoms. Both groups showed arteriosclerosis and, of course, some evidence of neuropathy, because they were selected for that reason. One can see that those two groups were similar to the group discussed in the present paper, and data relating to one group probably apply roughly to the others, although the patients reported on in this paper were somewhat older and had had diabetes somewhat longer. The fact that the blood cholesterol averages in the groups in the other paper were above normal, 267 and 236 mg., respectively, per hundred cubic centimeters, encourages us to believe that the chemical study of the nerves may be of importance.

For controls for the nerves from diabetic persons nerves were taken at autopsy from persons of various ages, with various diseases. These will hereafter be referred to as "normal nerves." Those used for analysis were the femoral nerves near the point of exit from the spinal cord. The extraneous tissue and fat on the outer surface of the epineurium of the nerve trunk were removed by dissection. This is not always easy, since the fat penetrates into the nerve, and this is one source of error in the determination of the total or neutral fat.

The extraction of the tissue was carried out by methods outlined by Bloor.[31] A weighed portion of the nerve was ground with clean sand and extracted with hot alcohol and then ether. The analyses for total lipid and phospholipid were carried out on aliquots of the alcohol-ether extracted by Bloor's methods. His technic for the colorimetric determination of total cholesterol by the Liebermann-Burchard reaction was also used. Cerebrosides were determined by Kimmelstiel's method.[32]

31. Bloor, W. R.: The Oxidative Determination of Phospholipid (Lecithin and Cephalin) in Blood and Tissue, J. Biol. Chem. **82**:273, 1929.

32. Kimmelstiel, P.: Eine Mikromethode zur Bestimmung der Cerebroside, in Festschrift zum 60. Geburtstag von Hofrat dr. Fritz Pregl, Leipzig, Emil Haim & Co., 1929.

Neutral fat is a derived value obtained by subtracting the fatty acids combined in phospholipids and cerebrosides from the total fatty acids. It is assumed in these calculations that the cholesterol is all in the free state, since only traces of cholesterol ester were found at any time.

Tables 1 and 2 give the results obtained. Phospholipids in the nerves from diabetic persons were a third of the normal value. Cholesterol and cerebrosides were approximately half as high in the diabetic as in the normal nerves. Neutral fat in the diabetic nerves averaged twice the normal value.

The wide variations in the so-called normal nerves were to be expected, because of the variety of material taken for analysis. The effects of age and various diseases on the lipid content of nerves are practically unknown. These effects could not be controlled in the normal nerves.

TABLE 1.—*Chemical Composition* of Nerves from Normal Persons*

Nerve	Neutral Fat		Phospholipid		Cholesterol		Cerebroside	
	Wet	Dry	Wet	Dry	Wet	Dry	Wet	Dry
Femoral	6.25	....	4.73	....	1.36	....	1.69	....
Femoral	7.59	....	4.69	....	1.39	....	0.92	....
Femoral	17.30	36.4	3.93	8.40	1.18	2.56	1.02	2.16
Femoral	7.60	23.8	4.34	13.63	1.39	4.35	1.50	4.70
Femoral	4.23	18.1	2.44	10.45	0.71	3.04	1.36	5.83
Femoral	4.04	14.5	3.84	13.80	1.06	3.82	1.79	6.45
Femoral	9.05	24.0	5.24	13.85	1.89	5.00	1.81	4.80
Femoral	6.76	23.9	4.48	16.40	1.40	4.25	2.38	8.63
Femoral	10.42	27.3	5.90	15.60	1.86	4.84	3.08	8.05
Average	8.35	24.0	4.40	13.15	1.36	3.98	1.73	5.80
Mean deviation	3.02	4.5	0.67	2.14	0.22	1.50	0.48	1.50
Standard deviation	4.24	6.43	0.91	2.69	0.34	2.44	0.63	1.80
Probable error	2.86	4.34	0.61	1.81	0.23	1.64	0.43	1.21

* In this and the following tables the values for the various constituents of the nerves are expressed in per cent, or grams per hundred grams of tissue.

It appears that the essential lipid constituents of the nerves from persons with diabetes have degenerated, as shown by the decrease in the phospholipid, cholesterol and cerebroside content.

The increase of neutral fat may be the result of decomposition of phospholipid and cerebroside, although a more likely explanation seems to be the incomplete removal of the fatty tissue surrounding and penetrating the nerve. The possibility of an infiltration of fat from an extraneous source is not excluded, especially in the cases of a high fat content, and cholesterol esters may or may not have increased during the degeneration. Only traces of cholesterol esters could be found.

Bloor, Okey and Corner [33] found that cholesterol esters varied inversely with the activity of the corpus luteum, a high content being

33. Bloor, W. R.; Okey, R., and Corner, G. W.: The Relation of the Lipids to Physiological Activity: I. The Changes in the Lipid Content of the Corpus Luteum of the Sow, J. Biol. Chem. **86**:291, 1930.

TABLE 2.—*Chemical Composition of Nerves from Diabetic Persons*

Nerve No.	Case No.	Sex	Age at Death or Amputation, Years	Duration of Diabetes Mellitus, Years	Control of Diabetes Mellitus	Arteriosclerosis	Cause of Death or Amputation	Neuritic Manifestations	Nerve Analyzed	Wet Weight			
										Neutral Fat, per Cent	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
1	2629	F	63.6	12.8	Poor	3+	Infection: gangrene	Knee jerks: right, absent; left, normal; ankle jerks: right, absent; left, absent	Right posterior tibial	10.57	0.89	0.35	0.32
2	2863	F	61.9	9.8	Fair	3+	Infection	Knee jerks: right, normal; left, normal	Left posterior tibial	6.08	1.48	0.62	1.31
3	3775	M	65.8	13.8	Good	3+	Infection: gangrene; nephritis	.....	Right femoral	4.07	1.94	1.11	0.34
4	.....	..	....	....	.....	...	.....	.....	Left femoral	3.20	1.59	0.54	0.63
5	6177	F	60.0	5.0	Good	2+	Infection	Knee jerks: sluggish; ankle jerks, absent	Right posterior tibial	9.41	1.62	0.56	0.74
6	9191	F	73.2	1.9	Good	2+	Intestinal obstruction	Knee jerks: normal	Left femoral	30.08	3.71	1.08	0.82
7	9827	M	52.0	1.3	Good	1+	Infection	.....	Left femoral	46.00	3.85	1.15	1.60
8	10791	F	73.1	10.8	Good	3+	Gangrene	Knee jerks: normal; ankle jerks: ?	Right posterior tibial	12.90	0.83	0.23	0.95
9	10803	F	79.8	2.0	.....	3+	Infection: gangrene	Knee jerks: right, absent; left, absent; ankle jerks: right, absent; left, absent	Left posterior tibial	33.45	0.73	0.16	0.13
10	10804	F	75.4	20.0	.....	3+	Infection	Knee jerks: sluggish; ankle jerks: absent; leg pain	Right femoral	14.65	3.94	1.22	1.13
11	10964	F	63.6	24.0	Good	2+	Infection	Knee jerks: sluggish; ankle jerks: absent	Right posterior tibial	56.37	1.60	0.54	0.63
12	10974	M	53.3	1.8	Good	3+	Infection	Knee jerks: right, absent; left, absent; ankle jerks: right, absent; left, absent	Left posterior tibial	4.95	1.22	0.48	0.76
13	11005	M	60.8	1.3	Good	2+	Gangrene	Knee jerks: right, normal; left, normal; ankle jerks: right, normal; left, normal	Right posterior tibial	11.86	1.20	0.48	0.28
14	11080	F	71.1	4.8	Poor	3+	Gangrene	Knee jerks: right, sluggish; left, sluggish; pupils: sluggish	Right posterior tibial	8.18	1.48	0.53	0.52
15	11082	F	68.3	0.8	Good	3+	Coronary thrombosis	Knee jerks: right, normal; left, normal; ankle jerks: right, normal; left, normal	Right femoral	12.95	3.16	0.89	1.85
16	.....	..	....	....	.....	...	.....	.....	Right sciatic	8.42	2.10	0.87	0.68
17	11106	F	66.7	14.0	Good	3+	Infection	Cramps in legs	Left posterior tibial	18.48	0.65	0.22	0.61
18	11108	F	73.0	10.0	Good	4+	Gangrene	Knee jerks: right, normal; left, normal; ankle jerks: right, absent; left, absent; pupils fixed	Right posterior tibial	14.10	1.40	0.45	1.46
19	11128	M	70.3	1.0	Poor	2+	Gangrene	Knee jerks: right, normal; left, normal; ankle jerks: right, absent; left, absent	Right posterior tibial	8.50	1.50	0.66	0.85
20	11144	M	63.0	4.5	Good	2+	Gangrene	Knee jerks: right, normal; left, normal; ankle jerks: right, sluggish	Left posterior tibial	7.35	1.12	0.50	0.83
Average										16.07	1.75	0.63	0.82
Mean deviation										10.40	0.79	0.24	0.33
Standard deviation										14.04	1.01	0.31	0.43
Probable error										9.47	0.68	0.21	0.29

characteristic of the degenerated gland. A decrease in the total cholesterol content may be compatible with an increase in the cholesterol ester. The decrease in phospholipid in this group of patients supports the hypothesis that the phospholipid content is a function of physiologic activity. Free cholesterol and cerebroside appear to vary directly with the activity of the tissue.

In an examination of the chemical findings with respect to clinical features, we noted some points of interest, although data based on such a small series may not be entirely reliable.

As table 3 shows, age alone seems to affect the results very little, in contrast to Marton's [34] observation that irritability of the nerves decreases as age increases. The highest phospholipid, the highest choles-

TABLE 3.—*Average Values with Respect to Age*

Age	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
50 to 60 years	2	2.54	0.82	1.18
60 to 70 years	11	1.58	0.61	0.75
70 to 80 years	7	1.94	0.62	0.85
Normal average		4.40	1.36	1.73

TABLE 4.—*Average Values with Respect to Arteriosclerosis*

Arteriosclerosis	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
1+ (slight)	1	3.85	1.15	1.60
2+	6	1.69	0.64	0.69
3+	12	1.67	0.60	0.77
4+ (advanced)	1	1.40	0.45	1.46
Normal average		4.40	1.36	1.73

terol and the fifth highest cerebroside value were observed in the second oldest patient, whereas the second lowest phospholipid and the lowest cholesterol and cerebroside content were encountered in the oldest patient. The range of ages lay between 52 and 79.8 years, and we have therefore divided the patients into three groups: from 50 to 60 years, from 60 to 70 years and from 70 to 80 years.

Arteriosclerosis may be an important factor, since the fat values other than those of cerebroside dropped as the arteriosclerosis increased. Yet it must be said that we had only one patient with 1 + arteriosclerosis and one with 4 + and that the difference between the moderate and the more advanced class was very slight. Table 4 shows the comparison.

34. Marton, S.: Ueber verminderte Nervmuskelerregbarkeit bei Diabetes, Wien. Arch. f. inn. Med. **16**:309, 1929.

Another way of demonstrating the relationship to vascular disease is to compare the results with circulatory deficiency in the lower parts of the legs as judged by the method described by McKittrick and Root.[35] It seems unlikely that the circulatory deficiency noted in the lower parts of the legs extended as high as the pelvis. One is more inclined to view this feature as merely added evidence of arterial disease, which itself affected the nerves at higher levels. The fall in the lipid values with the increasing circulatory disturbance is striking, as portrayed in table 5, but the difference is apparently due in part to the level of the section of the nerve examined.

TABLE 5.—*Average Values with Respect to Circulatory Deficiency in the Lower Parts of the Legs*

Circulatory Deficiency	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0	1	3.85	1.15	1.60
1+	4	2.59	0.85	1.01
2+	8	1.69	0.62	0.80
3+ (seven)	7	1.19	0.45	0.63
Normal average		4.40	1.36	1.73

TABLE 6.—*Average Values with Respect to Proximal and Distal Nerves*

Level of Nerve	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Pelvis	7	2.90	0.98	1.01
Lower part of leg	13	1.21	0.44	0.70
Normal average		4.40	1.36	1.73

Still another method of determining the effect of the vascular disease is to compare the values for the posterior tibial nerves with those for the femoral and sciatic nerves at the level of the pelvis, because, as is well known, the effect of arteriosclerosis is more evident in the distal than in the proximal parts. There is a marked decrease of the lipid content of the tibial nerves as compared with that of the upper nerve trunks. This is in line with the statement of Pryce [6c] that the posterior tibial artery seems peculiarly susceptible to arteriosclerosis.

This is in accordance with the statement that the ankle jerks are affected sooner and usually to a greater extent than the knee jerks. It also bears out the statement of Auché [4] and Woltman and Wilder [6x] that the distal portion of the nerve is more damaged than the proximal. In this connection, a comparison of the values for the femoral and sciatic nerves in case 11,082, in which the knee jerks and ankle jerks and sensation to pinprick were normal, is interesting.

35. McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1929.

The figures given in table 7, with the exception of the value for the cerebroside in the femoral nerve, are definitely below the average normal values, although the patient exhibited no neuritic manifestations. This suggests that changes occur in the nerves before clinical evidence of neuritis is noted. In table 8 it can be seen again that in spite of normal tendon jerks the nerve on which the reflex depends shows a considerable degree of change. As would be expected, the greater the clinical evidence of neuropathy, the greater the chemical change.

TABLE 7.—*Comparison of Femoral and Sciatic Nerves in Case 11,082*

Nerve	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral (right)	3.16	0.89	1.85
Sciatic (right)	2.10	0.87	0.68
Normal average	4.40	1.36	1.73

TABLE 8.—*Average Values with Respect to Absence or Normality of Reflex*

Condition of Reflex	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	4	2.54	0.83	0.91
Absent (exclusive of 2 cases)	5	1.40	0.51	0.80
Absence of both knee jerks and both ankle jerks	2	0.98	0.32	0.45
Normal average		4.40	1.36	1.73

TABLE 9.—*Average Values with Respect to Severity* of Diabetes*

Severity of Diabetes	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild (17 cases)	1.87	0.64	0.82
Moderate (3 cases)	1.39	0.59	0.81
Normal average	4.40	1.36	1.73

* There being no standard for judging the severity of diabetes, we have used the following arbitrary standard, with consideration of the rapidity of changes in the blood sugar, the size of the patient, etc.: mild, requiring no insulin or no more than 10 units a day, moderate, requiring from 10 to 30 units a day, and severe, requiring more than 30 units a day, with an adequate diet with from 120 to 180 Gm. of carbohydrate.

In comparing the chemical values with the diabetes itself, the fact that we classify the neuropathy as diabetic implies that the duration, the severity or the control of the diabetes should exert some influence on the changes noted. Marton [34] found decreased irritability of the nerves in proportion as the duration of the diabetes increased. As a matter of fact, the changes we noted seem only slightly dependent on these factors, possibly because we have too few cases for comparison. Nevertheless the results are compatible with the fact that diabetic neuritis is rarely observed in diabetic children, who are most severely afflicted with the disease and in whom the disease is less often well regulated.

The most that one can say about the effect of the diabetes is that those patients having the disease less than two years show less changes on the average than those having it longer; that those in whom the diabetes is mild show slightly less change than do the patients with a moderately severe case, and, finally, that those in whom the diabetes has been well controlled have average values more nearly approaching normal than the patients in whom the diabetes has not been properly regulated. But in each group marked variations occur at times, possibly owing to the influence of factors other than the diabetes and in particular to the level of the nerve section examined and the nerve used. Femoral nerves probably have a lipid content different from that of posterior tibial nerves.

TABLE 10.—*Average Values with Respect to Duration of Diabetes*

Duration	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0 to 2 years	8	2.18	0.72	0.87
2 to 10 years	5	1.42	0.53	0.97
10 to 24 years	7	1.62	0.60	0.66
Normal average		4.40	1.36	1.73

TABLE 11.—*Average Values with Respect to Previous Control* of Diabetes*

Control	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Good	14	1.86	0.65	0.87
Fair	1	1.48	0.62	1.31
Poor	3	1.29	0.51	0.56
Normal average		4.40	1.36	1.73

* For an estimation of the control of diabetes we have used our records plus statements from the patients as to previous glycosuria. Specimens taken at the time of admission are not reliable, because at such times the diabetes is upset by the condition leading to amputation or death. If the urinary sugar was less than 1 Gm. per hundred cubic centimeters or the blood sugar less than 200 mg. and no increase in the dosage of insulin or decrease in carbohydrates in the diet was made, the diabetes was considered adequately controlled. As a matter of fact, we do not know that the diabetes was well controlled in any case, because we have no record of repeated, daily blood tests and urinalyses over a long period prior to the amputation or autopsy. Even if the blood sugar is practically normal and there is no glycosuria, there may be abnormal fat metabolism as evidenced by hypercholesteremia. We do not wish to convey the impression that we believe the diabetes has no effect in the production of the neuritic changes.

SUMMARY AND CONCLUSIONS

1. The amounts of various lipid constituents of nerves from persons with diabetes were determined and compared with those of nerves from nondiabetic persons.

2. The phospholipid, cholesterol and cerebroside values of diabetic nerves were found to be considerably below the averages found in the "normal" nerves used for controls.

3. The greater the vascular disease present and the lower the level of the nerve examined, the more marked were the chemical changes.

4. The effect of the severity, duration and control (as judged by glycemia and glycosuria) of the diabetes was slight or vitiated by other factors.

5. Occasionally marked variation occurred, unexplainable on the basis of vascular disease or of the known features of the diabetes (case 10,804).

6. The lipoid abnormality appeared in the absence of clinical evidence of neuropathy, but the degree of the abnormality increased as the clinical signs of neuropathy progressed.

7. The small number of cases and the many variables make the deductions unreliable. Subsequent work is being carried on to correct this.

STUDIES ON THE CORONARY CIRCULATION

III. EFFECT OF INTRAVENOUS INJECTIONS OF DEXTROSE ON THE CORONARY CIRCULATION

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The intravenous administration of dextrose has become an important therapeutic procedure. The use of dextrose in shock accompanying coronary thrombosis and in other forms of medical shock is now rather widespread. Marvin [1] recently reported that injections of dextrose have been effective in the treatment of heart failure and cardiac disturbances brought about by diphtheria. Edwards and Page [2] showed that intravenous injections of dextrose produce marked improvement in the action of hypodynamic hearts of dogs suffering from hypoglycemia produced by insulin. Middleton and Oatway [3] found that diabetic patients suffering from anginal pains were frequently hypoglycemic or that the sugar level was below that usually found in diabetic patients. Root and Graybiel [4] reported that in some patients the anginal pains are relieved by the intravenous injection of a solution of dextrose (20 cc. of a 50 per cent solution). Strouse, Soskin, Katz and Rubinfeld [5] reported that in diabetic patients hypoglycemia induced either by insulin or by a diet low in carbohydrates produced deleterious effects on the heart and, in some patients, caused anginal pains. The administration of dextrose was found to improve the condition in some cases. Smith,

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1. Marvin, H. M.: Personal communication to the authors.

2. Edwards, D. J., and Page, I. H.: Observations on the Circulation During Hypoglycemia from Large Doses of Insulin, Am. J. Physiol. **69**:177, 1924.

3. Middleton, W. S., and Oatway, W. H.: Insulin Shock and the Myocardium, Am. J. M. Sc. **181**:39, 1931.

4. Root, H. F., and Graybiel, A.: Angina Pectoris and Diabetes Mellitus, J. A. M. A. **96**:925 (March 21) 1931.

5. Strouse, S.; Soskin, S.; Katz, L. N., and Rubinfeld, S. H.: Treatment of Older Diabetic Patients with Cardiovascular Disease, J. A. M. A. **98**:1703 (May 14) 1932.

Gibson and Ross,[6] working with nondiabetic patients suffering from cardiac failure, observed beneficial effects from the administration of an increased amount of carbohydrate. They attributed the improvement to the easily available energy of the carbohydrates. Sprague and Camp[7] used hypertonic solution of dextrose intravenously in the treatment of nineteen cases of cardiac disease. They reported good results in patients suffering from paroxysmal dyspnea and cardiac asthma. Reports of successful treatment of conditions involving circulatory disturbances by intravenous injections of dextrose are numerous.

It seemed to us that further experimentation for the purpose of determining the cause of the beneficial results following the administration of dextrose might be valuable. In our recent work on the effect of various chemical agents on coronary circulation, we have become interested in the length of time that the coronary circulation is influenced by the drug as well as by the amount of change produced. It would seem that the beneficial action of any drug used to improve coronary circulation would be derived from a sustained increase rather than from a sudden increase of short duration. Epinephrine produces a sudden and marked increase in the coronary flow, but the effect is very brief. Levine, Ernstene and Jacobson[8] found that patients suffering from angina pectoris experienced typical pains following the administration of epinephrine. Even though there is a sudden dilatation of the coronary vessels, observed experimentally following the administration of epinephrine, the constriction which follows seems to be the cause of the anginal pain in patients suffering from angina pectoris.

METHODS

Our first series of experiments was conducted on the whole animal under uniform ether anesthesia. The method was the same as that previously described by us.[9] The Morawitz cannula was somewhat modified in that the inner brass tube was transferred to the wall of the cannula, thus permitting a freer flow of blood and less likelihood of the formation of a fibrin clot in the cannula. Pure gum tubing with a wall thickness of 1/32 inch (0.08 cm.) was used for valve material. The valve was sufficiently short that no obstruction of flow into the sinus occurred except from the posterior cardiac vein.

6. Smith, F. M.; Gibson, R. B., and Ross, N. G.: The Diet in the Treatment of Cardiac Failure, J. A. M. A. **88**:1943 (June 18) 1927.

7. Sprague, H. B., and Camp, P. D.: Intravenous Hypertonic Glucose in the Treatment of Cardiac Disease, New England J. Med. **206**:288, 1932.

8. Levine, S. A.; Ernstene, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, Arch. Int. Med. **45**:191 (Feb.) 1930.

9. Ginsberg, A. M., and Stoland, O. O.: The Effect of Glycocyamine on the Coronary Circulation, J. Pharmacol. & Exper. Therap. **41**:195, 1931.

An anticoagulant from dog liver was used; larger amounts were necessary following the administration of dextrose on account of the increased coagulability induced by the dextrose. Control experiments have convinced us that by this method the coronary flow remains nearly uniform for at least forty minutes, provided the artificial respiration is properly adjusted. In our latest experiments, the blood pressure was maintained at a constant level by a compensator.

Experiments were carried out on twenty-eight dogs. The dextrose used was a 50 per cent solution. It was introduced through the return flow cylinder attached to the femoral vein. Injection at the rate of 2.5 Gm. per minute produced no appreciable change in the blood pressure. Determinations of the blood sugar were made by the Folin-Wu method.

The second series of experiments was conducted on the denervated heart-lung preparation described by Knowlton and Starling.[10] Several innervated heart-lung preparations, following the method of Anrep and Segall,[11] were also used.

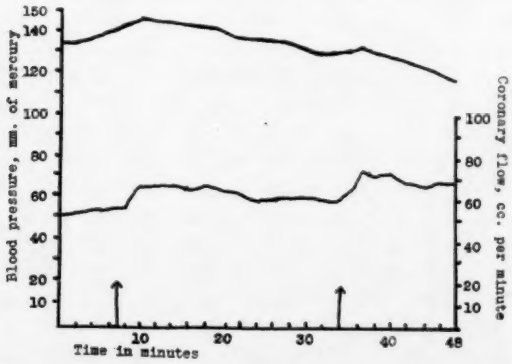

Fig. 1.—Blood pressure (upper curve) and coronary sinus flow (lower curve) in an intact animal. At the arrows 5 Gm. of dextrose (10 cc. of a 50 per cent solution) was injected, showing that a second injection of dextrose is as effective as the first in increasing the coronary circulation.

RESULTS

On the Whole Animal.—The results of our experiments on the whole animal are recorded in table 1. In figure 1 the results of a typical experiment show that the increased flow of blood from the coronary sinus occurs even when the blood pressure is somewhat lower than the preinjection level. In most of the experiments the blood pressure was slightly increased following the injection of dextrose.

It will be seen that the rate of output from the coronary sinus was increased in every case. The maximum increase occurred in from two

10. Knowlton, F. P., and Starling, E. H.: The Influence of Variations in Temperature and Blood-Pressure on the Performance of the Isolated Mammalian Heart, J. Physiol. **44**:206, 1912-1913.

11. Anrep, G. V., and Segall, H. N.: The Central and Reflex Regulation of the Heart Rate, J. Physiol. **61**:215, 1926.

to forty-one minutes after the injection of dextrose. In most of the experiments the amount of dextrose used was 5 Gm. in a 10 cc. solution. In most of them the coronary flow did not return to the preinjection level in forty minutes or more. When repeated injections were made, the second injection produced as great an increase as or even a greater one than that which followed the first injection. These results, we

TABLE 1.—*Effect of Dextrose on the Coronary Circulation of Intact Dogs**

Dog	Weight, Kg.	Date	Normal Coronary Flow, Cc. per Minute	Maximum Flow		Maximum Percentage Increase in Flow†	Amount of Dextrose Injected, Gm.	
				Cc. per Minute	Time After Injection, Minutes			
1	8.6	5/ 1	21	40	22	90.4	10	
2	10.0	5/ 8	28	47	5	67.8	10	
3	10.2	5/13	28	51	3	82.1	10	
4	5.5	6/10	20	52	6	160.0	10	
5	9.5	6/11	54	95	13	75.9	7	
6	8.2	6/13	26	38	3	46.1	5	
			32	50	8	56.2	5	(second injection)
7	10.5	6/14	41	60	5	46.3	5	
			41	62	11	51.2	5	(second injection)
8	....	6/15	28	35	4	25.0	5	
			28	44	6	57.1	5	(second injection)
9	6.4	6/16	24	43	3	79.1	5	
10	7.2	6/17	18	43	20	138.8	5	
11	10.4	6/18	44	72	16	63.6	5	
12	13.7	6/20	32	67	7	109.2	5	
13	8.2	6/21	39	90	41	130.7	5	
14	7.3	6/23	21	39	7	85.7	5	
15	8.2	6/24	35	74	32	111.4	5	
16	10.4	6/29	49	54	6	10.2	5	
			50	65	5	30.0	5	(second injection)
17	9.5	7/14	55	134	22	143.6	5	
18	10.0	4/21	33	74	14	124.2	5	
19	8.1	11/20	17	27	2	58.0	5	
			18	32	2	77.0	5	(second injection)
20	10.4	10/17	67	98	5	46.0	5	
			42	65	10	54.0	5	(second injection)
21	10.4	4/22	21	48	36	128.5	5	
22	9.5	4/24	30	38	2	26.6	5	
23	9.1	4/25	14	20	8	30.0	5	
24	10.9	5/ 2	18	25	2	28.0	5	
			21	39	7	85.7	5	(second injection)
25	8.5	5/ 4	37	60	7	62.1	5	
			39	64	5	64.1	5	(second injection)
26	9.3	8/18	23	26	9	13.0	5	
			25	29	3	16.0	5	(second injection)
27‡	9.5	8/17	41	55	4	31.8	5	
28‡	11.3	8/17	57	68	3	19.3	5	
			61	74	3	21.3	5	(second injection)
29‡	11.8	8/21	65	90	4	38.4	5	

* A 50 per cent solution of dextrose was injected intravenously at the rate of 5 cc. per minute.

† The average percentage increase in coronary blood flow with 5 Gm. of dextrose (twenty-four dogs) equaled 66.48 and on the second injection (ten dogs), 51.26. The average percentage increase in coronary blood flow with 10 Gm. of dextrose (four dogs) equaled 100.07.

‡ In this experiment the blood pressure was maintained at a uniform level near normal during the period of experimentation.

believe, are of paramount importance for they show that injections of dextrose do not render the coronary mechanism incapable of responding to the further administration of dextrose. The results point further to the possibilities of the intravenous administration of dextrose as a means of maintaining a sustained increased flow in the coronary circulation without noticeable changes in either the heart rate or the blood pressure.

The results of a typical experiment with repeated injections of dextrose are shown in figure 1. The amount of dextrose injected is apparently a factor in increasing the coronary circulation, since 10 Gm. usually produced a greater increase in flow than was produced by the injection of 5 Gm. In one experiment the injection of 25 Gm. of dextrose increased the coronary flow from 25 to 92 cc. per minute four minutes after the injection was completed.

These results seem to justify the following conclusions concerning the intravenous administration of dextrose as a means of increasing the coronary circulation in the intact animal: 1. The increase is very marked, ranging from 10 to 100 per cent or more. 2. The increased rate of flow is maintained for a long period, forty minutes or more. 3. Repeated injections continue to be effective in increasing the coronary flow.

Fig. 2.—Blood pressure and coronary sinus output of dog weighing 11.3 Kg. while under ether anesthesia. Between the arrows, 5 Gm. of dextrose (50 per cent solution) was injected intravenously. The figures on the baseline indicate the coronary sinus flow in cubic centimeters per minute. The blood pressure was maintained at a uniform level by means of a pressure compensator.

4. The amount and rate of injection produced no undesirable physiologic reaction, provided the rate of injection was not more than 2.5 Gm. per minute. In some of our experiments more rapid injections, up to 10 Gm. per minute, produced a temporary fall in blood pressure. In this experiment a fall of blood pressure from 80 mm. to 60 mm. of mercury occurred, but the blood pressure promptly returned to normal. These results indicate that when 50 per cent solutions of dextrose are administered intravenously, the injection should be made at a slow rate.

In three experiments, the blood pressure was maintained at a uniform level by means of a compensator. The results were not appreciably different from those in which the blood pressure was not controlled, and

indicate that the increased coronary flow following injections of dextrose could not be attributed to a change in the blood pressure. The results of such an experiment are shown in figure 2.

On the Denervated Heart-Lung Preparation.—The effect of dextrose on six heart-lung preparations was determined. The solution of dextrose was added to the blood in the venous reservoir in amounts equivalent to that used in the whole animal. The results obtained on the heart-lung preparations are recorded in table 2. In two of the experiments the coronary flow was slightly increased by the introduction of dextrose, but in the other four the flow was unaltered or decreased. In two of the experiments, when the heart rate was determined the rate increased at the same time that the coronary flow decreased following

TABLE 2.—*Effect of Dextrose on the Coronary Circulation of Denervated Heart-Lung Preparations.**

Experiment	Weight, Kg.	Date	Normal Coronary Flow, Cc. per Minute	Maximum Change in Flow		Maximum Percentage Change in Flow		Amount of Dextrose Injected, Gm.
				Cc. per Minute	Time After Injection, Minutes	Increase	Decrease	
1	19.0	2/21	42	47	12	11.9	....	1.5
2	23.6	2/22	34	37	4	8.8	....	1.5
3	16.7	3/21	40	40	..	....	....	1.5
4	10.2	3/28	51	42	11	....	17.6	1.5
			42	42	..	....	....	1.5 (second injection)
5†	22.2	6/28	97	86	10	....	11.4	1.5
			86	80	1	....	6.9	1.5 (second injection)
6†	17.1	6/29	100	85	12	....	15.0	2.5
			85	80	2	....	5.8	2.5 (second injection)
Average							4.0	

* A 50 per cent solution of dextrose was injected into the venous reservoir, except in experiment 2 in which the injection was given directely into the venous cannula.

† Changes in the heart rate were determined; the heart rate increased from 12 to 24 beats per minute after the injection of dextrose.

the injection. The results indicate that dextrose has no dilator action on the coronary vessels which could account for the increased coronary circulation in the whole animal.

Hydremia, caused by the hypertonic solutions of dextrose, might by decreasing the viscosity of the blood account for the augmented coronary flow in the whole animal. Kinsman, Spurling and Jelsma [12] and others have shown that there is a marked decrease in the specific gravity of the blood following injections of hypertonic solutions of dextrose. The fact that the specific gravity increased very suddenly and returned to normal twenty minutes after the injection of hypertonic solution while the increased coronary flow came on gradually and lasted much longer indicates that the increased coronary flow following the

12. Kinsman, J. M.: Spurling, R. G., and Jelsma, F.: Blood and Cerebro-Spinal Fluid Changes After Intravenous Injections of Hypertonic Solutions, Am. J. Physiol. **81**:165, 1928.

administration of dextrose in the whole animal cannot be fully accounted for by this factor.

The viscosity of the blood was determined in two experiments. There was a slight decrease in viscosity after the injection of the hypertonic solution of dextrose, but the viscosity soon returned to the preinjection level before the maximum coronary flow developed.

That the increased coronary circulation in the whole animal following the injection of dextrose is only partially accounted for by drawing fluids from the tissues into the blood was further demonstrated by the

TABLE 3.—*Effect of Dextrose on the Coronary Circulation in Innervated Heart-Lung Preparation.**

Experiment	Weight, Kg.	Date	Normal Coronary Flow, Cc. per Minute	Maximum Change in Flow		Maximum Percentage Change in Flow		Place of Injection of 1.5 Gm. Dextrose
				Cc. per Minute	Time After Injection, Minutes	Increase	Decrease	
1	17.2	7/30	41	45	1	9.7	....	Cerebral circulation
			42	46	2	9.5	....	Cerebral circulation (second injection)
			43	39	5	...	9.3	Cardiac circulation (third injection)
2	16.0	8/11	43	38	7	...	11.6	Cerebral circulation
			41	43	2	4.8	....	Cardiac circulation (second injection)
3	10.9	8/12	55	53	6	...	3.6	Cardiac circulation
			52	48	9	...	7.6	Cerebral circulation (second injection)
4	14.0	8/14	55	59	1	7.2	....	Cerebral circulation
			63	57	4	...	9.5	Cardiac circulation (second injection)
Average							1.15	
				After Cutting Vagi				
1	17.2	7/30	71	75	2	5.6	....	Cerebral circulation
2	16.0	8/11	97	105	1	8.2	....	Cerebral circulation
3	10.9	8/12	63	58	6	...	7.9	Cardiac circulation
Average							1.9	

* One and five-tenth grams of a 50 per cent solution of dextrose was injected as designated.

injection of isotonic solutions of sodium chloride and dextrose. In two experiments the injection of 100 cc. of a 0.9 per cent solution of sodium chloride caused practically no change in the coronary circulation; a corresponding injection of isotonic solution of dextrose in four animals produced an average increase of 34.2 per cent in the coronary circulation.

Hypertonic solution of sodium chloride (10 cc. of an 8 per cent solution) in five animals produced a 30 per cent increase in the coronary flow, while an equivalent amount of hypertonic solution of dextrose (50 per cent) produced an increase of 58.75 per cent in the coronary flow. These results indicate that the increased coronary flow following injections of dextrose cannot be fully accounted for by the hydremia and lowered viscosity of the blood. It is apparently one important factor.

On the Innervated Heart-Lung Preparation.—Several innervated heart-lung preparations were utilized to determine whether the improved coronary circulation following injections of dextrose was caused by the action of dextrose on the nerve centers. In these experiments the method described by Anrep and Segall [11] was used, except that the cerebral circulation was allowed to return directly to the heart. The cerebral circulation was maintained at a uniform pressure throughout the experiments, and the presence of the corneal reflex showed that adequate circulation was maintained through the brain. Sodium amytal was used as the anesthetic.

An increased coronary flow which followed cutting of the vagus nerves indicated that the tonic coronary constrictor action of the vagus mechanism was active during the experiment. The results obtained in these experiments are recorded in table 3. The amount of dextrose injected corresponded to that used in the denervated heart-lung prepara-

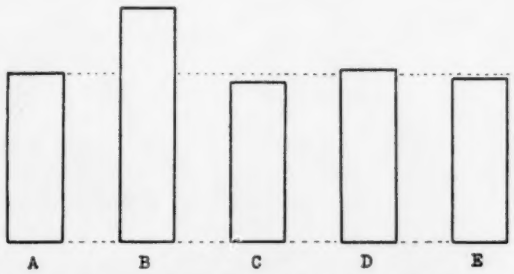

Fig. 3.—A comparison of the effect of injections of dextrose on the coronary flow: *A*, normal coronary sinus output; *B*, coronary sinus output ten minutes after an injection of dextrose into an intact animal; *C*, same as in *B*, for a denervated heart-lung preparation; *D*, same as in *B*, for an innervated heart-lung preparation; *E*, same as in *B*, for an innervated heart-lung preparation with both vagus nerves cut.

tions and was about equivalent to that used in the intact animal on the basis of the volume of circulating blood.

As will be seen from the table, there was no appreciable change in the coronary flow following the injections of dextrose into the cerebral or cardiac circulation. A slight increase occurred one or two minutes after the injection, when the coronary flow returned to the former level. These results show that the increased coronary flow in the intact animal following the administration of dextrose is not caused by the action of dextrose on nerve centers.

Comment.—A comparison of the normal coronary blood flow with the coronary flow of the intact animal and of the denervated and innervated heart-lung preparations following injections of dextrose is shown

in figure 3. These results show conclusively that dextrose has no direct effect on the coronary vessels or on the nervous centers. The improvement of the coronary circulation in the intact animals and in the various types of patients must be the result of other factors.

The blood sugar values were determined in a number of experiments. In three experiments we found an increase of 5.7 mg. per hundred cubic centimeters of blood in a ten minute period as a result of the ether anesthesia. Injection of an anticoagulant from dog liver in amounts equivalent to that used in the experiments on the coronary circulation produced a rise of 7.16 mg. of blood for a ten minute period. In control experiments on the coronary circulation, the blood sugar level rose 10.68 mg. in ten minutes. Following the injection of 5 Gm. of dextrose in the whole animal, which caused an increase in coronary circulation, the blood sugar level was increased an average of 75.2 mg. ten minutes after the injection. In heart-lung preparations, when we introduced dextrose in amounts equivalent to that used in the whole animal the blood sugar level increased 122.87 mg. per hundred cubic centimeters of blood ten minutes after the dextrose was added to the blood in the venous reservoir. Since the highest blood sugar level was attained in the heart-lung preparations, in which we found no increase in the coronary circulation, it is apparent that the high blood sugar level has no effect on the coronary vessels.

The improved coronary circulation observed in the intact animal is undoubtedly caused to a large extent by the increased water content of the blood. Since the increase does not occur in heart-lung preparations, it seems justifiable to assume that the hydremia is due to drawing water from the abdominal and other organs rather than from the heart and lungs. While our results do not prove conclusively that the entire increase is due to the hydremia of the blood, other possible causes have been ruled out. For some reason the hydremia produced by hypertonic solution of dextrose is more effective in increasing the coronary circulation than that produced by injecting hypertonic or isotonic solutions of sodium chloride.

SUMMARY AND CONCLUSIONS

1. The effect of intravenous administration of dextrose on the coronary circulation has been determined on the intact animal and on denervated and innervated heart-lung preparations before and after cutting of the vagus nerves.

2. Intravenous injection of 5 Gm. of dextrose in a 50 per cent solution produced a marked and sustained increase in the coronary circulation of the intact dog under ether anesthesia.

3. Hypertonic solution of dextrose in amounts equivalent to that used in the intact animal produces no significant change in the coronary flow of denervated or innervated heart-lung preparations.

4. Repeated injections of dextrose are effective in increasing the coronary flow of intact animals.

5. Part of the increase in the coronary flow can be accounted for by the increased water content of the blood, the water being drawn mainly from organs other than the heart and lungs.

6. That the increased flow is not due to a reflex involving the nerve centers is evident by the fact that in the innervated heart-lung preparations no increase in the coronary flow followed injections of dextrose.

7. The sustained increase in the coronary flow in the intact animal and the absence of undesirable physiologic reactions following the administration of hypertonic solutions of dextrose may account for many favorable clinical results reported and also suggest its use as a therapeutic agent for patients requiring improvement in the coronary circulation.

FRAGILITY AND MATURATION OF RETICULOCYTES

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The experimental observations reported here were designed to give additional information as to the relative ability of the reticulocytes to withstand such hemolytic substances as saponin in the living animal and in shed blood and to determine the rate and extent to which they mature into nonreticulated cells. These points were considered of importance in connection with the validity of the two current theories as to the origin of macrocytic hyperchromic (addisonian or pernicious) anemias. The maturation theory ascribes the disease to the absence of sufficient quantities of a substance needed for the maturation and release of the red cells; the hemolytic theory ascribes the disease to the action of an absorbed hemolytic agent. Since neither theory is adequately proved, it seemed desirable to know more about the properties of the curious vital-staining cells, the sudden increase of which, in spontaneous and induced remissions of macrocytic anemia, is such a significant phenomenon. Similar but less striking increases occur in anemia due to a deficient absorption of iron when iron is supplied. The reticulocytes are present in unusual numbers in all of the anemias known to be of hemolytic origin but are not numerous during relapses of primary anemia.

METHODS

Reticulocytes in abundance are present in the blood of rats kept for three or four days at barometric pressures of from 300 to 400 mm. of mercury. The blood, treated with an anticoagulant from dog liver or oxalate or defibrinated by being shaken with glass beads, was used for the study of hemolysis in vitro, and wet preparations stained with brilliant cresyl blue were used for reticulocyte counts. Washed red cells and varying amounts of plasma from the same animal were added to tubes with from 0.2 to 1.4 mg. of saponin per hundred cubic centimeters. The volume of cells was 0.2 cc.; the total volume in each tube was 2.5 cc. The smears were made from tubes showing partial hemolysis. The reticulocyte percentage was based on a count of at least 1,000 red cells.

Rabbits were used for the experiments on the action of saponin on the reticulocytes in circulating blood. The solution was injected intravenously, and reticulocyte counts were made on wet preparations of blood taken from the small ear veins at intervals thereafter.

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EXPERIMENTAL RESULTS

Resistance of Reticulocytes to Saponin and to Hypotonic Salt.—When the red blood cells of a rat are washed with a 0.9 per cent solution of sodium chloride three times and then suspended in weak saponin solutions at icebox temperature for from twelve to eighteen hours, there is a decrease in relative percentage of reticulocytes in the dilution in which partial hemolysis takes place. This also is observed in blood

TABLE 1.—*The Effects of Saponin During Twenty-Four Hours in the Icebox on the Percentage of Reticulocytes in the Blood* *

Blood	Concentration of Plasma, per Cent of Cell Volume	Concentration of Saponin, Mg. per 100 Cc.	Reticulocyte Count	
			Control, per Cent of Total Red Blood Cells	Saponin, per Cent of Total Red Blood Cells
Rat 1	0	0.4	14	2.2
Rat 2	0	0.6	4	1.8
Rat 3	0	0.9	14	9.5
	33	1.0	13	44.5
Rat 4	30	0.8	30	60
Rat 5	10	0.6	29	12
Rat 6	50	1.0	10.9	27
	25	1.0	10.4	30
	10	0.8	4	5
Rat 7	30	1.1	8.8	36
	0	0.6	9.0	7
	20	0.8	9.8	38
	10	0.9	8.4	27
Rat 8	200	0.8	82	100
	0	0.6	80	100
Johnson primary anemia	400	1.0	36	55
	0	0.8	38	7.3
MacMahon chlorotic anemia	300	1.0	5.2	4.2
	0	1.0	6.0	1.2
Rat 12 (37 C.)	30	1.0	11.0	4.2
Rat 13 (37 C.)	30	1.0	14.5	5.8

* Rat 2 was normal, and rat 8 had anemia due to Bartonella and splenectomy. All of the others had been under low barometric pressure for from four to six days. The patient's blood was obtained during the response to therapy. At the temperature of the icebox the reticulocytes were better protected by the addition of plasma to the saponin-cell mixture than were the mature cells. Saponin was added to whole blood from rats 12 and 13 and incubated for eighteen hours at 37 C. Plasma failed to protect the reticulocytes.

from anemic patients with reticulocytosis due to therapy. This is the reverse of the effect of hypotonic salt, which breaks up normal cells more readily than it does the reticulocytes. It is also the reverse of the effect when whole blood or washed red cells mixed with one-tenth their volume of plasma are added to saponin solutions. In the icebox plasma protects immature red cells from saponin more effectively than it does mature cells (table 1). Only in blood with the red cells damaged by Bartonella muris (anemia five days after splenectomy) were reticulocytes found to be more resistant to saponin than were the mature infected cells.

At 37 C. even the presence of the plasma fails to protect the reticulocytes from saponin. With both rat and rabbit blood the reticulocyte percentage falls when the blood which is taken with heparin or defibrinated is incubated with saponin under sterile precautions. At 37 C. citrate and oxalate in the weakest anticoagulant doses cause lysis of the reticulocytes, as has previously been noted [1] and confirmed by us. Citrated or oxalated whole blood keeps for several days in the icebox without a change in the reticulocyte count.

Effect of Saponin on Reticulocytes in Vivo.—The intravenous injection of from 0.2 to 0.5 mg. of saponin per kilogram into the ear veins

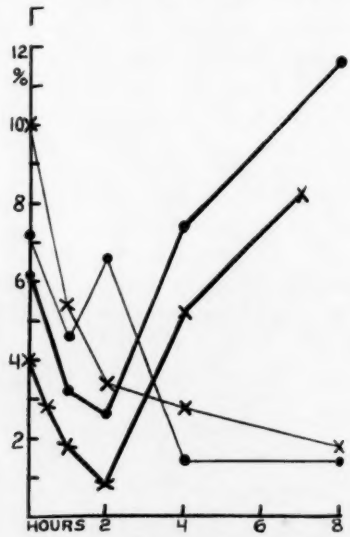

Fig. 1.—The effect of intravenous doses (0.5 mg. per kilogram) of saponin on the reticulocyte count of rabbits. The heavy lines indicate the first injection; the light lines, a second injection twenty-four hours later. Rabbit 1 is indicated by the dots; rabbit 2, by the crosses. The fall in the reticulocyte count begins and ends much more quickly with an initial than with a second injection. Recovery from the second injection began in from thirty to fifty hours.

of rabbits causes a rapid fall, followed by a rise, in reticulocytes. If the injection is repeated within twenty-four hours, the fall continues for from eight to twenty-four hours, instead of from two to three hours, as in untreated animals, and recovery to above the initial level occurs only after from twenty-four to thirty-six hours, instead of within from

1. Pepper, O. H. P.: Observations on Vitally Stainable Reticulation in Erythrocytes Preserved in Vitro, Arch. Int. Med. **30**:80 (Dec.) 1922.

four to eight hours. A rest of three days between injections results in rates of fall and rise intermediate between those on initial and those on second injection, with a twenty-four hour interval (fig. 1). This suggests that the lysis of reticulocytes in vivo is due to the activity of the animal tissues as well as to the drug, and that blocking the reticulo-endothelial cells as a result of the initial dose of hemolysant retards the speed of lysis and removal even when the effect of saponin has worn off and replacement of the reticulocytes has occurred. The importance of vital activity is seen when the rate of fall of the reticulo-

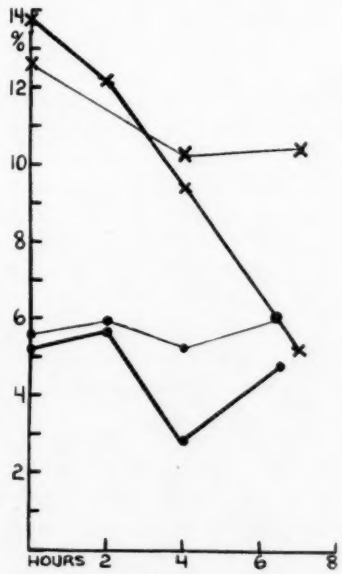

Fig. 2.—The comparative effect of intravenous doses of saponin on the reticulocyte counts of blood in vivo and in vitro. The heavy lines indicate in vivo; the light lines, in vitro. Five-tenth milligram of saponin per kilogram was injected immediately after the first in vivo count; in vitro counts were made at once and at intervals on 1 cc. of blood treated with an anticoagulant from dog liver drawn five minutes after saponin was given and incubated at 37 C. Rabbit 3 (indicated by dots) had an injection seventy-two hours before, and rabbit 4 (indicated by crosses), an injection forty-eight hours before; so that the fall in vivo is slower than that occurring with an initial dose, but much greater and faster than that in vitro.

cytes in the blood taken at intervals after an injection of saponin is compared with the rate of the fall in the blood taken five minutes after the injection and incubated in vitro. Doses of saponin which are effective

in producing a prompt fall in reticulocytes in vivo have no effect if incubated with blood in vitro or cause a rate of reticulocytic lysis which is much slower than that which occurs in the circulating blood (fig. 2).

Maturation of Reticulocytes in Vitro.—Four samples of defibrinated rat blood and three of blood from treated patients with primary anemia were incubated at 37 C. under sterile precautions. No evidence of the maturation of reticulocytes was found (table 2).

TABLE 2.—*The Percentage of Reticulocytes in Blood Incubated at 37 C. Without Bacterial Contamination* *

	Total Reticulocytes, per Cent	Old Forms, per Cent	Intermediate Forms, per Cent	Young Forms, per Cent
Rat A				
Fresh defibrinated blood	14.6	2	2.6	10
24 hours later	16.0	0	2.0	14
Fresh citrated blood	5.0	1	4.0	..
24 hours later	0.0	...	...	..
Rat B				
Fresh defibrinated blood	11.2	1.0	3.0	7.2
24 hours later	12.3	...	4.2	8.0
48 hours later	12.8	0.4	3.4	8.2
Rat C				
Fresh defibrinated blood	10.4	0.8	3.0	6.6
24 hours later	11.6	1.9	5.7	4.0
48 hours later	13.0	1.6	9.4	2.0
72 hours later	12.0	2.4	6.8	2.8
Rat D				
Fresh defibrinated blood	12.3	1.4	2.8	8.1
24 hours later	12.1	1.0	2.6	8.5
48 hours later	12.3	2.1	2.6	6.6
72 hours later	11.8	2.0	7.2	2.6
Smith (primary anemia)				
Fresh washed citrated blood cells plus fresh serum	16.6	3.2	11.6	1.8
24 hours later	12.4	8.0	4.0	0.4
Gill (primary anemia)				
Fresh defibrinated blood	28.5	5.7	17.1	5.7
8 hours later	28.0	7.6	16.4	4.0
24 hours later	33.0	1.2	29.0	2.8
72 hours later	28.6	(faint staining, differentiation impossible)		
L. P. (primary anemia)				
Fresh defibrinated blood	24.5	3.7	12.6	8.2
18 hours later	28.8	3.3	23.2	3.3
42 hours later	14.0	2.6	10.8	0.6

* There was no sign of maturation of young cells to old cells or of a change of reticulocytes to nonreticulocytes. The rats' polycythemic blood (counts 10,500,000 to 12,000,000) showed little serum after defibrination, while the blood from patients being treated with liver had a high plasma cell ratio. In rat A the effect of the citrate on the reticulocytes was in striking contrast with the effect of the incubation of defibrinated blood. The fresh smears stained much more rapidly than those from blood incubated more than twenty-four hours. The count on L. P., ten minutes after mixing, was only 2 per cent at forty-two hours, but rose to 14 per cent when the blood had stood more than thirty minutes.

These results contrast markedly with those of Heath and Daland,[2] who used smears made with brilliant cresyl blue dried on the slide. These investigators[3] later showed that this method does not give the

2. Heath, C. W., and Daland, G. A.: The Life of Reticulocytes: Experiments in Their Maturation, Arch. Int. Med. **46**:53 (Sept.) 1930.

3. Heath, C. W., and Daland, G. A.: Staining of Reticulocytes by Brilliant Cresyl Blue; Influence of Solutions of Substances, Arch. Int. Med. **48**:133 (July) 1931.

number of reticulocytes present but that it causes them to take up the stain easily. If one uses a wet method, as we did, the rate of staining is unimportant, as the counts are made within from twenty to thirty minutes after the cells and dye are mixed. Incubation alters the ease of staining, just as do the other methods of treatment, such as the salt solution method, which Heath and Daland studied. Hence an apparent decrease in the reticulocyte count is found when only a few seconds' staining time is permitted by the dry method.

COMMENT

Although casual mention of the fragility of reticulocytes in blood treated by anticoagulants has been made [1] and the increased fragility of blood containing young cells due to a low oxygen tension has been reported,[4] it is generally accepted that reticulocytes are immature but potentially sound cells. The fact that they resist hypotonic salt unusually well has created slight faith in their greater robustness. Although a few writers have regarded them as being fragile because they are immature, this has been an unsupported and unpopular notion.

We have confirmed the observation that the vitally staining red cells resist hypotonic salt and Bartonella better than do cells which do not take up the dye. We also confirmed the observation that the vitally staining red cells disintegrate more readily than do other red cells when exposed to isotonic citrate or oxalate solutions at 37 C.

In whole blood at 37 C., in suspensions of washed cells in the icebox, the greater fragility of reticulocytes in saponin solution is always apparent, but this is not true of whole blood at from 4 to 6 C. At a low temperature plasma protein protects the mature red cells less than it does the reticulocytes from saponin hemolysis. Mature washed red cells from rats with anemia due to Bartonella are also, at a low temperature, less resistant to saponin than are the reticulocytes. In dogs a prompt decrease in reticulocytes has been reported to follow intravenous injections of a saponin-like substance obtained from normal blood.[5]

In circulating rabbit's blood reticulocytes are far more easily destroyed by saponin injected intravenously than are the nonreticulated cells. The reticulocytes are not so rapidly destroyed when the blood treated with saponin is removed and incubated at body temperature as when the reticulocytes remain in the body. Concentrations of saponin

4. Kaulbersz, J., and Wischnowitzer, E.: Ueber die Resistenz der Blutkörperchen bei künstlich herabgesetztem Luftdruck, Ztschr. f. d. ges. exper. Med. **89:** 238, 1933; Resistenz der roten Blutkörperchen und die Zahl der Reticulocyten im Höhenklima, ibid. **87:**785, 1933.

5. Ucko, H.: Ueber die hämolytisch wirkenden Substanzen des menschlichen Blutes, Ztschr. f. klin. Med. **118:**22, 1931.

which are inert in shed blood incubated at 37 C. cause a rapid decrease in the reticulocytes in vivo. Hence it is necessary to invoke the action of the reticulo-endothlial system to explain the difference in behavior of saponin-treated blood in vitro and in vivo. In every experiment in which hemolysis affected reticulocytes more than nonreticulocytes, the younger (heavily staining) cells were affected more than the old (faintly staining) reticulocytes.

Since reticulocytes are more easily destroyed than other red cells in vitro or in vivo, by various substances, some of which, like citrate and oxalate, do not have an effect on normal cells, it becomes difficult to determine whether a decrease in reticulocytes or in younger forms (since these are most susceptible) is due to destruction or maturation. In defibrinated rat blood incubated under sterile precautions for from

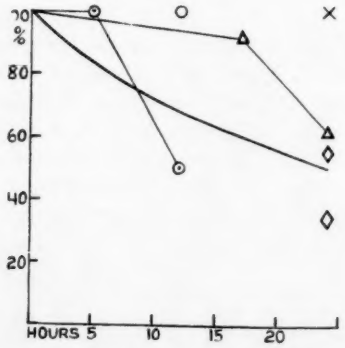

Fig. 3.—The decrease in reticulocytic concentration, given in terms of per cent of the initial level, in defibrinated blood incubated at 37 C. under sterile precautions. The heavy line is the theoretical curve, based on the assumption that 50 per cent of the reticulocytes mature every twenty-four hours. The fine lines indicate the distribution of recorded data. Pepper's findings are indicated by the triangles; Buckman and MacNaugher's (J. Med. Research **44**:61, 1923), by the circles; Denecke's (Ztschr. f. d. ges. exper. Med. **36**:179, 1923), by the circles and dots; Heath's, by the diamonds, and Mermod and Dock's, by the cross. Two observers found no evidence of maturation or destruction of reticulocytic loss. This suggests that the change in reticulocyte count was due to lysis by the accumulation of metabolic products rather than to maturation.

two to three days there is no change in the percentage of reticulocytes or in the proportion of young and old forms, and the published records of the changes in incubated blood of man and other animals shows that no change occurs within the first five to twelve hours (depending on the observer), with a rapid fall thereafter (fig. 3). This is undoubtedly different from the logarithmic curve of growth or maturation, and suggests that with incubation toxic substances may accumulate to

which reticulocytes, especially the young forms, are more susceptible than red cells in general. The change in the proportion of young and old forms, after the peak of rise in the treatment of primary anemia, may also be due to the relatively short survival time of young reticulocytes.

There are strong reasons for doubting whether maturation of reticulocytes in the circulating blood of man or animals occurs at an appreciable rate. The observation that rats with anemia due to deficiency in iron have reticulocytic showers (up to 1,000,000 per cubic millimeter) for two weeks when given copper alone, without a rise in the red count during this period, speaks against the classic 50 per cent maturation each twenty-four hours.[6] In the experiments of Morris and others on the injection of gastric juice in man, they noted prolonged high reticu-

TABLE 3.—*Fall in Nonreticulocytic Cells During the Reticulocytic Shower* *

Observer	Day of Therapy	Nonreticulocytic Red Blood Cells, Millions	Reticulocytic Red Blood Cells, Millions	Actual Loss of Nonreticulocytic Cells, Millions	Calculated Loss of Nonreticulocytic Cells, Millions in 24 Hours
Minot, Murphy and Stetson: A. J. M. Sc. **175**: 581, 1928	3	1.0	....	....	....
	7	....	(27%)	....	....
	8	0.9	0.5	0.1	0.235
Riddle and Sturgis: Am. J. M. Sc. **180**: 1, 1930	0	0.69	....	....	....
	3	....	(30%)	....	....
	4	0.50	0.62	0.12	0.35
Goldhamer, Isaacs and Sturgis: Am. J. M. Sc. **186**: 84, 1933	2	1.56	0.23	....	....
	3	1.44	0.56	0.12	0.23
	4	1.02	0.85	0.42	0.70
Goldhamer, Isaacs and Sturgis: Am. J. M. Sc. **186**: 84, 1933	2	0.93	0.10	....	....
	3	0.80	0.36	0.13	0.18
	4	0.68	0.55	0.12	0.30
	5	0.64	0.61	0.04	0.31

* Based on data published by various observers. The "calculated" daily loss of nonreticulated cells is based on the assumption that 50 per cent of the reticulocytes mature every twenty-four hours.

locytosis, with no significant rise in the red cell count until after the reticulocyte count began to fall. Even in older experiments with liver, it was apparent that the greater the reticulocytosis, the less the concomitant rise in the red count, although a rapid rise in the red count occurred later. The steep rise in the red count occurs here, as with injections of gastric juice, only after the reticulocyte count begins to fall. During the rise in reticulocytes, the count of nonreticulated cells actually falls in cases in which the reticulocytosis is sharp and marked (table 3). Since the excretion rate of bile pigment also falls rapidly when the reticulocytic peak is reached,[7] it seems unlikely that hemolysis

6. Elvehjem, C. A., and Schultz, M. O.: The Relation of Iron and Copper to Reticulocyte Response in Anemic Rats, J. Biol. Chem. **102**:357 (Oct.) 1933.

7. Farquharson, R. F.; Borsook, H., and Goulding, A. M.: Pigment Metabolism and Destruction of Blood in Addison's (Pernicious) Anemia, Arch. Int. Med. **48**:1156 (Dec.) 1931.

is occurring at the rate required by the theory that 50 per cent or more reticulocytes are maturing and being hemolyzed each day. These clinical data, with our observations on the fragility of reticulocytes, suggest that they rarely mature in the circulating blood, but have a short period of survival. Recovery from anemias of various sorts is accompanied or preceded by a brief shower of reticulocytes, but recovery occurs in spite of this premature launching of fragile and short-lived cells, not because of it.

CONCLUSIONS

The reticulocytes, and particularly the young (heavily stained) ones, are more easily destroyed in shed blood and in the circulating whole blood by saponin (and by citrate and oxalate in whole shed blood) than are the other red cells.

The maturation of reticulocytes in the circulating blood is not proved; it seems not to occur on any significant scale.

The occurrence of a reticulocytic crisis early in the treatment of anemia is probably an unavoidable evil associated with a change in the structure and function of the bone marrow. This precedes and delays the rise in the red cell count.

TULAREMIA

A CONSIDERATION OF ONE HUNDRED AND TWENTY-THREE CASES, WITH OBSERVATIONS AT AUTOPSY IN ONE

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It is my purpose in this paper not to review to any extent the literature pertaining to tularemia but to report a study of 123 cases of tularemia coming under my personal observation and, incidentally, to add new clinical and pathologic material to the known facts concerning an interesting and comparatively new disease.

HISTORY

Tularemia has the distinction of being a truly American disease. American investigators not only discovered its specific etiologic agent and its modes of transmission from animal to animal and from animal to man but described completely, for the first time, its bacteriology, pathology and clinical manifestations.

McCoy,[1] in 1911, contributed the first scientific knowledge of the disease by his description of a "plague-like disease of rodents" which he encountered while investigating a plague among ground squirrels in California. In 1912, the causative organism was identified by McCoy and Chapin [2] and given the name Bacillus tularense, after the county of Tulare, Calif., in which its discovery was made. During this same year, Chapin [3] demonstrated for the first time agglutinins of the organism in his own blood and in that of a laboratory attendant. They had just recovered from a febrile illness which, in the light of present knowledge, is recognized to have been tularemia. In 1914, Vail [4] and

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The material used in this article was presented as a part of the Scientific Exhibit at the Seventy-Ninth Annual Session of the American Medical Association at Philadelphia in June 1931, and at the Eighty-First Annual Session of the Medical Society of the State of Pennsylvania at Scranton, October 1931.

1. McCoy, G. W.: A Plague-Like Disease of Rodents, Pub. Health Bull. **43**:53, 1911.

2. McCoy, G. W., and Chapin, C. W.: Bacterium Tularense the Cause of a Plague-Like Disease of Rodents, U. S. Pub. Health & Mar. Hosp. Bull. 53, 1912, p. 21.

3. McCoy, G. W., and Chapin, C. W.: Further Observations on a Plague-Like Disease of Rodents with a Preliminary Note on the Causative Agent, Bacterium Tularense, J. Infect. Dis. **10**:61, 1912.

4. Vail, D. T.: Bacillus Tularense Infection of the Eye, Ophth. Rec. **23**:487, 1914.

Wherry and Lamb [5] of Cincinnati reported the first case in a human being to receive bacteriologic confirmation by the isolation of the organism. Wherry [6] also isolated the organism from a wild cottontail rabbit found dead. Under the title "A New Bacterial Disease of Rodents Transmissible to Man," Wherry [7] first called attention to its infectivity for man. Francis,[8] in 1919 and 1920, working in Utah, recognized the identity of "deer fly fever" and "plague-like disease of rodents" and named the disease tularemia because of the prevalence in the blood of Bacterium tularense. With Mayne [9] he demonstrated the agency of Chrysops discalis in transmission. His article entitled "Tularemia Francis 1921: A New Disease of Man" [10] is one of the really great classics of medical literature. In 1925, Novy unearthed a letter written in 1907 by Ancil Martin, an ophthalmic surgeon in Arizona, in which he called attention to 5 cases in human beings occurring in his practice. Francis' article also focused attention on an article written in 1911 by Pearse,[11] in which he described clinically, under the title "Insect Bites," 7 cases in human beings which he observed in Utah, where the disease became popularly known as "deer fly fever." Ohara,[12] in 1925, reported a fatal disease of wild rabbits in Japan which was proved by Francis and Moore [13] to be tularemia. In 1928, Russian workers [14] reported a series of cases

5. Wherry, W. B., and Lamb, B. H.: Infection of Man with Bacterium Tularense, J. Infect. Dis. **15**:331, 1914.

6. Wherry, W. B., and Lamb, B. H.: Discovery of Bacterium Tularense in Wild Rabbits, and the Danger of Its Transfer to Man, J. A. M. A. **63**:2041 (Dec. 5) 1914.

7. Wherry, W. B.: A New Bacterial Disease of Rodents Transmissible to Man, Pub. Health Rep. **29**:3387, 1914.

8. Francis, E.: Occurrence of Tularemia in Nature as a Disease of Man, Pub. Health Rep. **36**:1731, 1921.

9. Francis, E., and Mayne, B.: Experimental Transmission of Tularemia by Flies of the Species Chrysops Discalis, Pub. Health Rep. **36**:1738, 1921.

10. Francis, E.: Tularemia Francis 1921: A New Disease of Man, J. A. M. A. **78**:1015 (April 8) 1922.

11. Pearse, R. A.: Insect Bites, Northwest Med. **3**:81 (March) 1911.

12. Ohara, H.: Concerning an Acute Febrile Disease Transmitted by Wild Rabbits: A Preliminary Report, Jikken Iho, March 12, 1925 (Japanese text).

13. Francis, E., and Moore, D.: Identity of Ohara's Disease and Tularemia, J. A. M. A. **86**:1329 (May 1) 1926.

14. Golov, D. A.; Kniazevsky, A. N.; Berdnikov, V. A., and Tiflov, V. E.: Plague-Like Infections (Tularemia?) in the Region of the Basin of the Oural in the Spring of 1928, Rev. de microbiol., d'épidémiol et parasitol. **7**:301, 1928. Nikanorov, S. M.: Tularemia in North America and Tularemia-Like Disease in U. S. S. R., ibid. **7**:289, 1928. Suvorov, S. V.; Wolferz, A. A., and Voronkova, M. M.: Plague-Like Lymphadenitis in the Rayon of Astrakhan, ibid. **7**:293, 1928. Wolferz, A. A.: Tularemia-Like Disease on the Banks of the Oka in 1928, ibid. **7**:299, 1928.

contracted from handling the European water vole. In 1929, McNabb [15] reported the first case appearing in Canada. It was first recognized in Norway [16] in 1930, and in Sweden [17] in 1932. Laboratory workers have acquired the disease in England.

It is interesting that tularemia was known to have existed in rabbits in Kentucky prior to 1910 and that the disease occurred in man as early as 1907. My father, a practicing physician, advised me as early as 1910 not to hunt rabbits because of a fatal epizootic among them at that time. He also reported that there had been similar plagues occurring in rabbits at intervals over a period of twenty years and that he considered the disease contagious to man.

As early as 1907, Dr. Cowley of Berea, Ky., observed 2 cases of typical tularemia contracted by members of a family by handling the same rabbit. Agglutination of Bact. tularense in these cases is in dilutions of 1 : 120 at the present time.

ETIOLOGY

Distribution and Incidence.—Tularemia is a widespread disease, endemic in most communities and at certain seasons epidemic. The natural distribution of the disease in the United States is that of its carriers, the wood ticks Dermacentor Andersoni Stiles, Dermacentor variabilis and Dermacentor occidentalis Newmann. Shipment of infected rabbits was the cause of the disease in certain states. Cases in human beings were reported from forty-three states of the United States and from the District of Columbia. The disease was described in Japan in 1925, in Russia in 1928, in Norway in 1929, in Canada in 1929 and in Sweden in 1932.

Although cases of natural infection in human beings occur in every month of the year, the seasonal prevalence of ticks (from March to August) and of flies (from June to September) and the game laws protecting rabbits tend to control the seasonal incidence of the disease. The incidence of the disease in Kentucky is almost entirely controlled by epizootics in cottontail rabbits, which occur cyclically, at irregular intervals and under conditions as yet imperfectly known. The explanation of the interepidemic periods is not altogether satisfactory because sporadic cases occur then.

Sex, Race and Age.—Men and women are equally susceptible to the disease. Among the patients considered in this study there were 69

15. McNabb, A. L.: Tularemia: First Case Reported in Canada, Canad. Pub. Health J. **21**:91, 1930.

16. Thjøtta, Theodore: Three Cases of Tularemia: A Disease Hitherto Not Diagnosed in Norway, Norsk mag. f. lægevidensk. **91**:224, 1930; Tularemia og dens forekomst i Norge, Saertryk f. nord. med. tidskr. **2**:177, 1930.

17. Granström, K. O.: Tularemia Oculoglandularis, Acta ophth. **10**:237, 1932.

males and 54 females. Race did not play an important rôle; 14 cases were observed in Negroes.

Immunity.—Not all persons exposed to infection contract the disease. The long persistence of agglutinins in the blood of patients who have recovered may be an indication of their immunity. No instance of a second attack has been recorded.

Contagion.—Surgeons who have incised or excised suppurating glands have not contracted the infection. Members of patients' families, whose aseptic technic was nil, have dressed primary lesions and suppurating nodules and glands innumerable times without contracting the disease. Harris [18] reported a case in which a mother is thought to have acquired the disease as a result of pricking her thumb while dressing the tularemic ulcer of her son, who had been bitten by an infected deer fly. There is a possibility that in a case of my knowledge the infection was transmitted by the bite of a fly which had previously had access to pus from suppurating glands of an infected human being.

Distribution in the Body.—That an early bacteremia exists in man is made manifest not only by the occurrence of typical foci of necrosis in the spleen, liver and lungs but by the recovery of the organism from the blood as early as the third day and as late as the twelfth day of the illness. The organism has not been recovered from the blood after the twelfth day. During life, cultures have been obtained from pleural effusion, ascitic fluid, sputum, lymph glands, primary ulcers and spinal fluid. At autopsy, the organism is found widely distributed, in greatest number and most constantly in the regional lymph glands (axillary, cervical and submaxillary), lungs, liver, spleen and blood.

Bacteriology.—Bact. tularense is a small pleomorphic organism, gram-negative, nonmotile and nonspore-bearing. It grows under aerobic conditions. The optimum temperature is 37 C., and the optimum p_H range, between 6.8 and 7.3. It causes fermentation in mediums containing dextrose, levulose, mannose and glycerin, forming acid but not gas. It grows well on coagulated egg yolk and blood dextrose cystine agar, but not on ordinary laboratory mediums. Bacillary, coccoid and bipolar forms are noted. In smears it stains well with crystal violet or aniline gentian violet, and in sections of animal tissue it stains best with Giemsa's solution. Foshay and his co-workers [19] demonstrated the presence of the organism in sections of human tissue from 2 fatal cases of tularemia. A temperature of from 56 to 58 C. kills the organism in cultures and in spleen tissue in ten minutes. Cultures suspended in saline

18. Harris, C. E.: Tularemia, M. Sentinel **32**:6, 1924.

19. Fougler, M.; Glazer, A. M., and Foshay, L.: Tularemia: Report of Case with Postmortem Observations and Note on Staining of Bacterium Tularense in Tissue Section, J. A. M. A. **98**:951 (March 19) 1932.

solution containing 0.1 per cent of a dilute solution of formaldehyde, U. S. P. (37 per cent), are rendered nonvirulent after twenty-four hours. Spleen tissue rubbed in 1 per cent cresol is free from virulence after two minutes. Pure, undiluted glycerin into which cultures or spleen tissue is placed preserves the virulence for one month at room temperature, for six months at 10 C. and for one year at —14 C. Treatment with glycerin in conjunction with annual or semiannual animal passage serves to perpetuate the virulence of a strain for years. Spleen tissue frozen at less than — 14 C. loses its virulence in one month. Prolonged refrigeration of cultures on a medium of coagulated egg yolk greatly reduces their virulence for certain laboratory animals.

Frozen rabbits are infective for three but not for four weeks. The virus resists drying in bedbug feces for twenty-six days.

For its propagation in nature, Bact. tularense, as far as is known, depends entirely on the wood ticks Dermacentor Andersoni Stiles, Dearmacentor variabilis and Dermacentor occidentalis Newmann, which bite both rabbits and man. The hereditary transmission of the organism by female wood ticks to their eggs, larvae and nymphs establishes this host as a permanent reservoir of infection.

Other blood-sucking insects—lice, flies and ticks—are believed to transmit the infection from animal to animal in nature.

MORBID ANATOMY

While the individual lesions grossly and histologically simulate those of tuberculosis, the pathologic process as a whole has a certain distinctiveness.

Focal areas of necrosis in various stages of evolution are the essential lesions in the body tissues. Following the primary insult there is a cellular reaction consisting of polymorphonuclear leukocytes and epithelioid cells, often enmeshed in fibrin. As the lesion advances necrosis occurs in the center, and a marginal zone of epithelioid and fibroblastic granulation tissue in radial arrangement appears. In older lesions, this is further surrounded by a peripheral zone of lymphocytes with cells of the Langerhans type.

REPORT OF A CASE

The characteristic pathologic anatomy can best be described by presenting the observations in a fatal case of the primary ophthalmic type of the disease coming to autopsy on the twelfth day of the illness.[20]

Macroscopic Examination.—The body was that of a well developed and well nourished Negro about 40 years of age.

Eyes: The lids of the right eye were moderately edematous. The palpebral conjunctiva was diffusely covered by a thick, grayish-yellow, fibrinopurulent mem-

20. Autopsy was performed by Dr. E. S. Maxwell, Department of Pathology, the Lexington Clinic.

brane measuring from 1 to 2 mm. in thickness. This membrane also extended over the bulbar conjunctiva to the cornea, where it stopped abruptly. The surface of the membrane was rather irregular, but no definite ulcers were recognized. Considerable material was easily scraped from the surface, but the membrane was closely adherent to the deeper structures. The iris, lens, vitreous and retina were apparently normal. The left eye showed no gross lesions.

Glands: The preauricular, superior cervical and submaxillary glands on the right side were enlarged. The glands of the hilus of each lung, as well as the mediastinal glands, were moderately enlarged. The mesenteric and retroperitoneal glands were moderately enlarged, measuring from 5 to 10 mm. in diameter.

Thorax: The viscera of the thoracic and abdominal cavities were completely transposed.

Lungs: The lungs were bound down posteriorly by numerous fibrinous and fibrous adhesions between the visceral and the parietal pleura. Many small petechial hemorrhages were scattered over the pleural surfaces, particularly on the diaphragmatic surface and between the lobes. The right pleura presented a thin, delicate, fibropurulent membrane over the dependent portion. Diffusely scattered throughout both lungs were numerous small, discrete, miliary and confluent tubercles varying from 1 to 10 cm. in diameter. On section, the larger areas were gray and presented softened centers. Both lungs showed moderate edema in the dependent portions.

Cardiovascular System: The pericardium was smooth, and the cavity contained no excess fluid. The heart, except for a complete transposition of all anatomic structures, showed no unusual features.

Peritoneum: The peritoneum was covered by a thin, delicate, fibrinopurulent exudate, and a small excess of turbid fluid was present in the cavity. The peritoneal coat of the appendix presented more exudate than the peritoneum in general.

Liver: The liver was slightly larger than normal, and the surface of the cut section was rather cloudy. A moderate number of small grayish-yellow lesions, averaging about 1 mm. in diameter, were seen beneath the capsule and on the cut section. An occasional larger confluent mass of grayish tissue was found. The gallbladder presented no abnormalities.

Spleen: The spleen was not enlarged, weighing 110 Gm. The capsule was thickened and was covered by a thin fibrinopurulent exudate. The surface of the cut section showed numerous minute yellowish opaque spots with cleancut margins.

Kidney: The left kidney was approximately normal in size. No changes were seen in the capsule. The capsule stripped readily. The surface of the cut section showed a definite cloudiness in the cortex. The lining of the pelvis was smooth. The ureter was grossly normal. The right kidney and ureter were similar to the left. The pancreas showed no gross lesions. The suprarenal glands were grossly normal.

Other Organs: The mucosa of the stomach and of the small and large intestines did not show evidence of disease. The bladder, prostate gland and testicles showed no gross lesions.

Histopathologic Examination.—Glands: The preauricular and cervical lymph nodes showed miliary and confluent areas of caseous necrosis surrounded by a zone of endothelial cells containing many foreign body giant cells. The submaxillary salivary gland tissue showed no distinctive pathologic condition. The lymph nodes of the hilus of each lung and of the mediastinal, mesenteric and retroperitoneal tissues showed areas similar to those noted in the preauricular and cervical glands.

Eyes: The conjunctiva and cornea were covered with a heavy layer of lymphocytic and polymorphonuclear infiltration surrounding multiple foci of early caseous necrosis. The inflammatory exudate and foci of necrosis entirely replaced the squamous epithelium. The ciliary body, choroid and retina were not involved.

Lungs: Sections from the small nodules in the lungs showed areas of acute caseous necrosis with complete destruction of the alveolar walls. Many of these areas of necrosis were not associated with the bronchi or bronchioles. There were acute passive congestion and edema. The pleura was covered with a fibrinopurulent exudate, on the surface of which was a layer in which the nuclei of all cells were degenerated.

Liver: The liver showed numerous areas of miliary focal necrosis. The smaller areas involved only a few liver cells, while the larger ones involved several lobules. The larger foci had caseous centers. A thin area of fibrinous exudate was found on the peritoneal surface of the liver. The liver cells showed moderate cloudy swelling.

Spleen: In the splenic parenchyma were many areas of acute caseous necrosis, many of which were confluent and formed large lesions. The capsule was covered with a thin layer of fibrinopurulent exudate.

Peritoneum: The peritoneum showed an infiltration of lymphoid cells with decided pyknosis and degenerative changes in the cells of the outer portion.

Kidneys: The kidneys showed slight degenerative changes in the epithelium of the convoluted tubules. The glomeruli were intact.

Other Organs: The suprarenal glands, pancreas, testicles, prostate gland and bladder showed no abnormalities.

TYPES OF INFECTION

The classification preferred and used entirely in this report is as follows:

1. Primary cutaneous tularemia (ulceroglandular and glandular tularemia), in which the primary lesion is a papule of the skin, later an ulcer, and is accompanied by enlargement of the regional lymph glands. In rare instances the primary lesion is absent at the site of infection but there is enlargement of the regional lymph glands. Ohara [21] proved by inoculation of a human being that this can occur.

2. Primary ophthalmic tularemia (oculoglandular tularemia), in which the primary lesion is a conjunctivitis and is accompanied by enlargement of the regional lymph glands.

3. Cryptogenetic tularemia (typhoid type), in which Bact. tularense enters the body without causing any cutaneous lesion or local manifestation. This is the type usually presented by laboratory workers.

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21. Ohara, H.: Human Inoculation Experiment with a Disease of Wild Rabbits with a Bacteriological Study, Kinsei Igaku, vol. 12, no. 5, 1926 (Japanese text).

SOURCES OF HUMAN INFECTION

There are many ways by which the disease may be transmitted from an infected host to man. While wild rabbits and wood ticks (Dermacentor Andersoni Stiles) constitute the important reservoirs of infection

Fig. 1.—Bilateral primary ophthalmic tularemia with regional adenopathy and subcutaneous nodule, four weeks after onset.

for other animals and man, other animal hosts and transmitters (the woodchuck, opossum, muskrat, skunk, European water vole, cat, coyote, quail, sheep, hog, gray and red squirrel, ground squirrel and European marmot, insect vectors, such as the deer fly [Chrysops discalis] and ticks

[Dermacentor variabilis, Dermacentor occidentalis Newmann]) have been sources of infection in various localities.

In this series of cases the sources of infection were as follows:

1. For primary cutaneous tularemia with regional glandular enlargement (102 cases): One patient had associated with sheep and ticks. One had been bitten by a fly (Stomoxys calcitrans). Ninety-two had handled or dressed wild rabbits. One had been bitten by an opossum. One had skinned an opossum. One had skinned a red squirrel. Two had been bitten by a cat. One had had an open wound licked by a cat. One had crushed rabbit lice on his hand. One had picked ticks from a dog.

2. For primary cutaneous tularemia without a primary lesion but with regional glandular enlargement (6 cases): All the patients had dressed wild rabbits.

3. For primary ophthalmic tularemia (6 cases): All the patients had dressed wild rabbits.

4. For cryptogenetic tularemia with no initial lesion, regional glandular involvement or local manifestations (9 cases): One patient had picked ticks from a dog. All the others had skinned and dressed wild rabbits.

MULTIPLE INFECTION

Three members of one family contracted tularemia of the primary cutaneous type by handling the same rabbit. Double infections occurred in 13 instances, the primary cutaneous type occurring in both members of the family in 7 instances; the primary cutaneous type in one member and the cryptogenetic type in the other, in 4 instances, and the primary cutaneous type in one member and regional glandular involvement without a primary lesion in the other, in 2 instances.

PERIOD OF INCUBATION

The average period of incubation, definitely determined in 58 cases in which there was a single exposure to infection, was four and one-half days. The incubation period could not be determined in all cases.

SYMPTOMS AND GENERAL COURSE

Although extraordinarily variable in its local manifestations, the mode of onset and the general constitutional reaction in the various types of tularemia are identical. Complications at the onset or during the course of the disease may alter the general characters.

The constitutional disturbance in cases of mild tularemia is slight, and there are instances of extensive local disease without grave systemic symptoms. More commonly, the onset is sudden, often occurring while

the patient is at work, and is manifested characteristically by headache, vomiting, chilliness, chills, aching bodily pains, sweating, prostration and fever.

During the active stage, which lasts from two to three weeks, fever, weakness and prostration, chilliness, recurring chills and sweats, aching pains in the back and extremities and loss of weight are the usual symptoms. Delirium and stupor may be present in the more severe cases. Following the onset of the primary cutaneous type of the disease, the patient may note that a previous cut or sore is acutely inflamed and painful or that a small, raised, red papule makes its appearance where hitherto there was no cut or abrasion. Within from thirty-

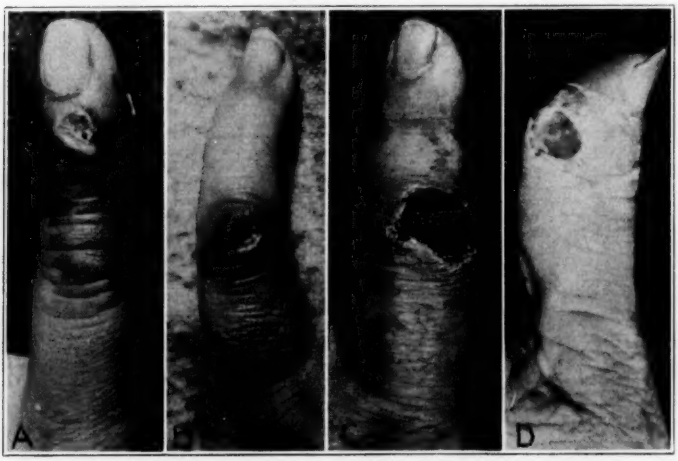

Fig. 2.—Primary cutaneous lesions of tularemia: *A*, a primary papule on the seventh day; *B*, a primary papule showing beginning liberation of the necrotic core on the fourteenth day; *C*, a primary ulcer after liberation of the necrotic core on the twenty-first day; *D*, a primary ulcer on the forty-second day.

six to forty-eight hours after the onset, the regional lymph glands may be slightly enlarged and tender. Pain is complained of in this region frequently before attention is called to the primary lesion. Painful red streaks may be seen extending from the primary lesions toward the regional glands, or vice versa.

In cases in which a regional adenopathy occurs without a primary lesion, the constitutional reaction and course are the same.

In the cryptogenetic type, the onset, course, constitutional symptoms and duration of the disease are the same as in the other types.

In the ophthalmic type, the primary localization is in the conjunctival sac. It occurred bilaterally in 1 of the 6 cases observed. The early sub-

jective local symptoms are itching, swelling of the lids (accompanied by lacrimation), photophobia and pain. Almost simultaneously the preauricular, parotid, submaxillary and cervical glands become swollen, tender and painful. In severe cases, the axillary glands may be involved. If the patient is seen shortly after the onset, the conjunctiva presents the picture of acute conjunctivitis, chemosis is pronounced and the conjunctiva is a vivid scarlet. The lids are decidedly swollen. Small, discrete, yellow nodules (measuring from 1 to 6 mm. in diameter) appear soon on the chemotic conjunctiva of both lids. Rarely, single nodules appear on the bulbar conjunctiva, which at this time is edematous and injected. In 2 cases, the palpebral and bulbar conjunctivae were covered by a gray, translucent, organized exudate which ended abruptly at the cornea. In 1 case

Fig. 3.—Suppurating adenopathy four weeks after onset.

in which there was bilateral ocular involvement the conjunctivitis was equally severe in the two eyes, but nodules did not appear in the conjunctiva of one eye, and the inflammatory reaction subsided much more rapidly. The regional adenopathy in this case was unilateral. In another case, no nodules or definite ulcers were noted, but there seemed to be an irregular pitting in the inflamed conjunctiva. The small necrotic nodules tend to break down, leaving small punched-out ulcers which eventually heal without leaving a scar. There is a mucowatery or mucopurulent discharge, usually straw-colored, which is at first moderately profuse and lessens in amount as the local condition improves. The active conjunctivitis continues from three to five weeks, then the swelling gradually recedes. A solitary subcutaneous nodule was present on the cheek in 1 case. The glands may remain small and nodular or become greatly enlarged, the enlargement persisting for many months or

progress to suppuration. Suppuration occurred in 5 of the 6 cases of primary ophthalmic tularemia. A papular eruption appeared on the same side of the face and neck during the first week of the disease in 1 case.

SPECIAL FEATURES

Pulmonic Tularemia.—Pulmonic tularemia is another manifestation of the hematogenous dissemination of the disease. A review of the autopsy observations in cases of death from tularemia is significant. Invariably the essential pulmonic lesion is tularemic focal necrosis surrounded more or less by a zone of lobular pneumonia. Bact. tularense has been repeatedly isolated from these lesions. The character of the invading organism is responsible for this pathologic condition. In 1928, Bunker and Smith [22] isolated Bact. tularense from the sputum during the twelfth day of the illness and from the lungs and other tissues at autopsy. During the same year, I [23] called attention for the first time to a case of primary pulmonic tularemia. Sixteen cases in this series presented distinct pulmonary involvement characteristic of the variable clinical findings noted in bronchopneumonia. Nine cases occurred in association with the primary cutaneous type of the disease. In 7 cases the symptoms were primarily pulmonic (cryptogenetic type), beginning abruptly with fever, dyspnea, cough and sometimes pain in the chest. In 4 of these cases, one other member of the family had the primary cutaneous type of the disease from handling the same rabbit. Death occurred in 4 cases, indicating a mortality of 25 per cent in pulmonic tularemia.

Pulmonic symptoms may usher in the onset or appear some time during the course of the disease. More often, the usual symptoms of onset of pulmonic tularemia are increase in the fever and pulse rate, severe cough and shortness of breath. Pleurisy with effusion was observed at the onset in 3 cases. During the course of the disease, a distressing cough, increasing dyspnea and cyanosis are important clinical features. Delirium and stupor may occur in the more severe cases.

As a rule, both lungs are affected, but the clinical signs generally are more extensive in one lung than in the other. Physical signs may vary from day to day, suggestive signs disappearing and reappearing later or being replaced by fresh signs in other locations. The physical signs may at first be those of capillary bronchitis, as indicated by the presence of fine crepitant and sibilant râles and the absence of dulness to percussion. After a few days medium moist, sticky râles may appear over the lower lobes posteriorly, and one can recognize areas of

22. Bunker, C. W. O., and Smith, E. E.: Tularemia: Report of Four Cases, One Fatal, with Autopsy Report, U. S. Nav. M. Bull. **26**:901, 1928.

23. Kavanaugh, C. N., in discussion on Francis.[24]

impaired resonance in haphazard patches or, when the patches of bronchopneumonia have merged, actual dulness. The breath sounds may be harsh, but they are not definitely tubular. If numerous foci involve the greater part of a lobe the breathing may be tubular and may be mistaken for that of lobar pneumonia. The sputum is usually scanty and tenacious but seldom bloody or rusty. The course is variable; the disease may be fulminant, the patient dying in from four to twelve days, or it may persist after the febrile course of the disease. The areas of consolidation clear up slowly and often remain for a long time after the constitutional symptoms have disappeared.

Primary Cutaneous Lesion.—A primary lesion occurred on the finger or hand in 102 cases. It was single in 87 cases and multiple in 15 and

Fig. 4.—A solitary subcutaneous nodule and multiple primary lesions on the fingers.

occurred bilaterally in 11. The largest number of primary lesions in any case was five. Neither its multiple nor its bilateral occurrence seemed to have any effect on the degree of severity of the other symptoms. The initial lesion appears within from three to seven days after inoculation, and it first manifests itself as a small, painful, inflamed papule which gradually enlarges and on breaking down liberates a necrotic core, leaving an ulcer with raised edges and a punched-out appearance which has a grayish-red necrotic base which is exquisitely sensitive. The size attained is variable, and when small the sore may be overlooked, particularly if the patient is not seen early in the course of the disease. Ulcers on the dorsum of the hand are usually more shallow than those on the palmar surface where the skin is thicker. It must be emphasized that the infection may occur without any decided primary lesion or with only a superficial erosion or ulceration. Absence of a

history of an initial lesion is of no value in excluding the possibility of infection. The size of the ulcer is decidedly increased following surgical incision, and an exacerbation of general symptoms follows each incision. The discharge is scanty and serous. The ulcer heals slowly and is replaced by scar tissue. Incision of the primary lesion materially lengthens the time required for its healing.

Subcutaneous Nodules.—Subcutaneous nodules occurred in 28 instances. They were found on either the anterior or the posterior surface of the forearm or arm, and occasionally they extended from the primary lesion to the enlarged axillary glands. In 1 case of the primary ophthalmic type, a single nodule was noted on the cheek. These nodules are at first firm and movable; later they frequently become attached to the skin, and many of them ultimately suppurate. In the cases in this series they varied in size from that of a pea to 1 cm. in diameter, and their number varied from one to thirty. In several instances con-

Fig. 5.—Multiple subcutaneous nodules on the hand and arm.

glomerate masses of nodules (nodular lymphangitis) 10 cm. long by 3 cm. wide were observed. Pain was noted only in the cases in which suppuration occurred.

Glandular Involvement.—In a small percentage of the cases lymph glands other than the regional glands were slightly enlarged and tender. In 3 cases in which the axillary glands were primarily involved the submaxillary glands on the same side were visibly enlarged. Unilateral enlargement of the axillary glands was noted in 1 case of the ophthalmic type. Enlargement of the epitrochlear glands associated with axillary adenopathy was noted in several cases. In 33 cases (29.5 per cent) the glands suppurated and after the inflammation had subsided either were incised or ruptured through a soft, thin, bluish-red spot in the skin. In the rest of the cases the glands did not break down but remained hard, palpable and rather tender for from three to twelve months, gradually returning to normal. Suppuration of lymph glands was noted four, and even twenty-four, months after the disease.

Suppuration of regional glands was not necessarily accompanied by suppuration of nodules, but in all cases in which there was suppuration of nodules the regional glands also broke down.

Cervical Adenitis.—Four cases presented a unilateral enlargement of the cervical glands without a primary lesion or other local manifestations. In 2 of these cases one other member of the family was suffering from primary cutaneous tularemia, the primary lesion having been contracted from handling the same rabbit. The glands were suppurative in 2 of the 4 cases. No lesions were noted in the mouth or throat.

Cutaneous Eruption.—A cutaneous eruption was observed in 23 cases (18.7 per cent). It usually appeared during the second or third week

Fig. 6.—Left primary ophthalmic tularemia with regional adenopathy and complicating dacrocystitis.

and lasted from a few days to three or four weeks. It occurred most frequently on the arms and neck, was always bilateral and in most instances was symmetrically distributed.

The polymorphism of the eruption is so marked that it is practically impossible to designate a characteristic lesion, the eruption being macular, papular, vesicular or pustular or any transitional form from one of these types to another. Evolution was seldom complete in these lesions. Involution was usually by absorption or exfoliation.

The essential characteristics, along with a bacteremia, suggest that such eruptions are the result of toxins in the circulation or of local invasion of bacteria.

In 2 cases lesions typical of erythema nodosum were noted on the shins and thighs. Herpes was noted on the buccal mucous membrane in several cases.

In a double infection from the same rabbit, two contrasting types of eruption were noted: in one case a papular type which terminated in absorption; in the other, a maculopapular eruption which terminated in a brawny desquamation. In 3 cases during the course of the disease, a pronounced acne developed on the back and shoulders. No scarring or pigmentation was noted after the disappearance of the eruption in any case.

Changes in the Blood.—Secondary anemia is common, with a red cell count of between 3,500,000 and 4,000,000 and a hemoglobin content of 70 per cent. The blood smear shows achromia of red cells. Early in the disease a leukopenia (white cell count from 5,000 to 7,000) is common, but sometimes the count is higher, frequently normal. A polymorphonuclear leukocytosis of from slight to moderate degree (from 12,000 to 15,000 cells) may occur during the course of the disease.

Fever.—The temperature records were not particularly characteristic in the few cases in which complete charts were available. Continuous high temperature was noted in cases with extreme toxemia. Francis,[24] viewing 11 complete temperature charts for cases of the cryptogenetic type of the disease, was struck by the constancy of the sequence of initial rise, remission and secondary rise. The whole febrile course usually lasts from two to three weeks. Recurring mild attacks of fever were noted as late as ten months after the disease.

Splenomegaly.—Splenomegaly occurred in approximately 20 per cent of the cases. The enlargement, when evident, is not great; as a rule, a firm, tender edge is felt just below the left costal border. On rare occasions (5 cases) the spleen became large enough to extend three or four fingerbreadths below the costal margin. In these cases there was a subjective complaint of pain in this region and decided pain and tenderness were elicited on palpation (perisplenitis).

Tularemia in Children.—Eight children with ages ranging from 6 to 12 years were observed. The mode of infection in these cases is of interest. One child killed a rabbit with his slingshot, 4 handled a rabbit which their dog had caught, 2 cleaned a rabbit that their dog had treed in a rock fence, and 1 caught an adult rabbit with his hands.

Tularemia in Pregnancy.—Three patients contracted tularemia during pregnancy and were delivered of normal babies during the height of the infection. In 1 case labor was premature. The general course of the disease did not differ from its usual trend.

Ambulatory Tularemia.—Although the onset may be severe a large percentage of patients are about and attend to their work throughout the whole attack.

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24. Francis, E.: Symptoms, Diagnosis and Pathology of Tularemia, J. A. M. A. **91**:1155 (Oct. 20) 1928.

COMPLICATIONS

Ocular Disturbances.—In only 1 case was there any permanent impairment of vision; an early papilledema was present which resulted in atrophy of the optic nerve and loss of vision in the involved eye. In a case reported by Magath and Yater [25] there were blindness of the affected eye following perforation of the cornea, protrusion of the iris and fusion of the cornea and iris into a compact mass.

A purulent dacryocystitis was noted in 1 case.

Complications in the Breasts.—In 2 female patients a nodular lymphangitis extended from the axillary adenitis along the outer border of the pectoralis muscle and involved the breast. One of these patients was referred for amputation of the breast because of a suspected malignant condition. In each there was suppuration of the axillary glands and nodules of the breast necessitating wide incision and drainage.

Fig. 7.—Bilateral primary ophthalmic tularemia on the fifth day of the disease.

Thrombi in the Veins.—Thrombi occurred in only 1 instance. In this case both femoral veins were involved. The occurrence was manifested by a chill, pain and swelling along the veins, a rise in temperature and edema of the extremities. Recovery was complete.

Pericarditis.—Pericarditis is extremely rare. Simpson [26] reported 1 case in which an effusion was present.

Pleurisy.—Pleurisy occurred in 6 cases. In each instance it occurred with the onset. A pleural effusion was present in 3 cases.

Pneumothorax.—Pneumothorax is rare. It occurred during convalescence in 1 case of the primary cutaneous type, presumably as a result of a ruptured focal abscess.

25. Magath, T. B., and Yater, W. M.: Three Cases of Tularemia, M. Clin. North America **10**:745, 1926.

26. Simpson, V. E.: Tularemia: A Consideration Based on a Résumé of the Literature and Personally Observed Cases, with a Report of an Unusual Complication, Ann. Int. Med. **2**:1092 (April) 1929.

Abdominal Symptoms.—Abdominal pain and tenderness were noted in 5 cases and were present only at the onset. Operation for appendicitis was performed at the onset in 1 case of the primary cutaneous type because of iliac pain on the right side. The appendix was apparently normal. Parker and Spencer [27] observed these symptoms in several cases of the cryptogenetic type. In a case reported by Whiteis and Anthony [28] general abdominal pain was pronounced, and appendicitis as a complication was considered.

Peritonitis.—One case of the primary ophthalmic type presented symptoms of general peritonitis. At autopsy there was a diffuse peritonitis. A case of tularemic peritonitis was reported by Fulmer and Kilbury [29] in which Bact. tularense was isolated from the ascitic fluid. Francis [24] reported a case with diarrhea and intestinal hemorrhages during the last ten days of illness. At autopsy there was general peritonitis with a plastic exudate covering the abdominal contents. Fulmer [30] reported a death occurring on the twelfth day with symptoms of general peritonitis.

Disturbances of the Nervous System.—Delirium occurred in 6 cases, 4 of which terminated in death. In 2 of these cases the patients recovered in spite of advanced delirium and stupor during the course of the disease. During the first week of illness in 1 case an acute mania developed which persisted for several months. Recovery was complete. Hartman [31] reported his observations at autopsy in a case of acute tularemia with diffuse encephalitis. Bryant and Hirsch [32] recently reported a fatal case of tularemic leptomeningitis. Haizlip and O'Neil [33] reported a case of meningitis due to Bact. tularense, the organism being isolated from the spinal fluid.

Disturbances of the Urinary System.—The urine is usually diminished at first and has the ordinary febrile characters.

Osseous System.—Osteomyelitis of the femur occurred during convalescence in 1 case.

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27. Parker, R. R., and Spencer, R. R.: Six Additional Cases of Laboratory Infection of Tularemia in Man, Pub. Health Rep. **41**:1341, 1926.

28. Whiteis, W. R., and Anthony, E. J.: Tularemia in Iowa, J. Iowa M. Soc. **16**:188, 1926.

29. Fulmer, S. C., and Kilbury, M. J.: Tularemic Peritonitis, J. A. M. A. **89**:1661 (Nov. 12) 1927.

30. Fulmer, S. C.: Tularemia, J. Arkansas M. Soc. **24**:61, 1927.

31. Hartman, F. W.: Tularemic Encephalitis: Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, Am. J. Path. **8**:57, 1932.

32. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis: Report of Case, Arch. Path. **12**:917 (Dec.) 1931.
Tularense, J. A. M. A. **97**:704 (Sept. 5) 1931.

33. Haizlip, J. O., and O'Neil, A. E.: Case of Meningitis Due to Bacterium

DIAGNOSIS

The most important factor in the diagnosis of tularemia is to have the disease in mind. In infections in human beings the fact that one has dressed or dissected wild rodents, especially wild rabbits, or has been bitten by a tick or fly, with a primary cutaneous lesion or conjunctivitis with regional glandular involvement and characteristic onset symptoms suggests tularemia. In every doubtful case of fever the possibility of tularemia should be considered for this is the only outstanding symptom in the cryptogenetic type of the disease. A more difficult question to decide is whether an existing bronchopneumonia is simple or tularemic.

The intradermal test, suggested by Wherry [34] in 1917 and developed by Foshay [35] in 1932 is the earliest available diagnostic aid for determining the presence of tularemia. The reaction may become positive as early as the fourth day of the disease, practically a week before the

Fig. 8.—A solitary nodule involving the ocular conjunctiva on the twentieth day after the onset.

agglutinins usually appear in the blood. The test is specific and reliable, and the reaction becomes negative only when convalescence is complete.

The diagnosis can be confirmed further by obtaining an agglutination of Bact. tularense by blood serum collected in the second week of illness and by noting an increase in the agglutination titer in serum collected a few days later or in the third week, or by isolation of Bact. tularense from the guinea-pigs inoculated with material taken as early as the first week from the primary lesion or from the enlarged glands or the blood of the patient. The significance of a positive intradermal or agglutination test in the early diagnosis of tularemia is apparent, since it may be the only positive evidence of the disease. Microscopic examination of cover glass preparations taken direct from the patient is useless.

34. Wherry, quoted by Lamb, F. W.: Ophth. Rec. **26**:221, 1917.

35. Foshay, L.: Tularemia: Accurate and Earlier Diagnosis by Means of Intradermal Reaction, J. Infect. Dis. **51**:286, 1932.

Fig. 9.—Right primary ophthalmic tularemia with regional adenopathy on the tenth day after the onset.

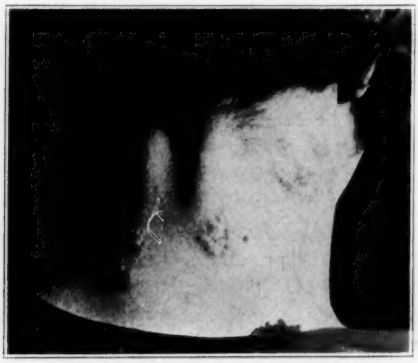

Fig. 10.—Annular patches on the neck with secondary crusting and scaling on the seventeenth day after the onset.

The Agglutination Test.—Specific agglutinins invariably appeared in all cases considered for this paper. The agglutinins are absent in the first week of the disease; they are always present at some time during the second week (1 : 10 to 1 : 160). In 2 cases agglutinins did not appear until the third week. During the third week there occurs an abrupt rise in the agglutinin titer, which reaches its maximum (1 : 1,280 or 1 : 2,560) from the fourth to the seventh week. The titer usually falls during the eighth week, gradually declining thereafter until at the end of the first year the average is about 1 : 160. Agglutinins have never entirely disappeared in any case, even from ten to twenty-four years after recovery.

Cross-Agglutination.—The frequent cross-agglutination of Bacterium abortus and Bacterium melitensis by serums from known cases of Bact. tularense infections, and the fact that serums from human patients with undulant fever may show cross-agglutination of tularense may leave some doubt as to the proper interpretation of the serologic findings. Tularemia serum in most instances agglutinates Bact. tularense in much higher dilution than those in which it agglutinates Bact. abortus or Bact. melitensis. In rare instances the employment of agglutinin absorption tests may be of value.

Differential Diagnosis.—The signs and symptoms of tularemia are so similar to those of many other acute infectious diseases, notably influenza, typhoid, undulant fever and septicemia, as to make differential diagnosis difficult. Because of subcutaneous nodules, sporotrichosis has been suspected. Pathologists have called the malady tuberculosis because of the lesions in the lymph glands. When the disease is epidemic and typical cases are occurring, the possibility of tularemia should always be borne in mind. In the case of the primary cutaneous type of the disease the typical primary lesion with regional glandular involvement should easily differentiate it from other diseases. Any prolonged, unexplained fever should suggest the possibility of tularemia. Primary atypical pneumonia in a locality where tularemia is prevalent should direct one's suspicion to the primary pulmonic type of the disease.

Heretofore any unilateral conjunctivitis with regional lymphadenitis was called Parinaud's conjunctivitis. A striking similarity and the absence of an established cause lead me to believe that many of the cases were actually instances of conjunctivitis tularensis. In 1924, Pascheff [36] suggested the substitution of the term "syndrome Parinaud" in place of "Parinaud's conjunctivitis" as signifying a unilateral conjunctivitis with regional adenitis.

Necrotic infectious conjunctivitis (Pascheff) is clinically similar to ophthalmic tularemia in many particulars. The acceptance of this disease as a clinical entity is not universal because of its close clinical

36. Pascheff, C.: Differential Diagnosis Between Conjunctivitis Necroticans Infectiosa and Conjunctivitis Tularensis, Am. J. Ophth. **10**:737, 1927.

similarity to ophthalmic tularemia, and because agglutination tests with Bact. tularense have not been carried out.

The morphologic and cultural differences between the two organisms seem definitely to differentiate the two diseases. On the other hand, the striking similarity of the ocular and clinical symptoms and of the characteristic histopathologic changes lead me to believe that primary ophthalmic tularemia and necrotic infectious conjunctivitis are one and the same disease.

Leptothrix conjunctivitis, although clinically similar, differs as to etiology, Leptothrix being found in the pus and necrotic nodules.

Sporotrichosis is readily differentiated by its cultural characteristics.

Fig. 11.—An erythema multiforme-like eruption on the hands and face on the fourteenth day after the onset.

CONVALESCENCE

Weakness in proportion to the severity of the attending toxemia is an outstanding feature of the course and convalescence. Following a severe clinical course it is rare to see a patient at full time labor within three months. In my experience, a mild clinical course was noted in the majority of cases. Sixty-three per cent of the patients were either continuously ambulatory or able to be up and about within from thirty-six to forty-eight hours following the onset. Only 25 per cent were doing less than 50 per cent of their work at the end of three months. At the end of six months 10 per cent were unable to perform more than half time work, and at the end of one year, 7 per cent were 25 per cent incapacitated because of fatigue and weakness.

DEATHS

Five cases (4 per cent) terminated in death. One case of the primary ophthalmic type with early pulmonary involvement, marked toxemia and stupor terminated in death on the twelfth day of the disease. In a second case, of the cryptogenetic type, with primary pulmonic involvement, extreme toxemia, delirium and stupor, the patient died on the fourteenth day of illness. Coma accompanied by albuminuria

Fig. 12.—Discrete elevated erythematous patches on the extensor surfaces of the arms three weeks after the onset.

Fig. 13.—A desquamating maculopapular eruption on the extensor surface of each arm on the twentieth day after the onset.

and casts was the terminal condition in another case of the cryptogenetic type, death occurring during the ninth month. Death in the fourth case was preceded by a spontaneous pneumothorax, and occurred on the thirtieth day, following sudden acute pain in the chest. This was a case of the primary cutaneous type of the disease. In the fifth case, one of the primary cutaneous type of the disease, the patient manifested early pulmonary symptoms, delirium, stupor and cyanosis and died on the twenty-sixth day. The death rate in this series compares closely with previously reported figures.

PROPHYLAXIS

Prophylaxis practically narrows down to the education of the public as to the dangers of the infection and the manner in which it is acquired. During an epidemic the early recognition of the disease in rodents is most important. Thorough cooking destroys the infective agent. The wearing of gloves by those who handle rabbits protects them to a certain extent. There have been 24 infections in laboratory workers in spite of all precautions.

Preventive Inoculation.—Prophylactic vaccination against tularemia was successfully accomplished by Foshay.[37] Such vaccination is not practicable for general use, but its apparent success recommends its use for those who come in close and frequent contact with infected animals.

TREATMENT

The patient should be at rest in bed during the febrile stage of the disease. Large subcutaneous or intravenous injections of physiologic solution of sodium chloride seem best to allay the symptoms of delirium and severe toxemia. Healing of the primary cutaneous lesion does not seem to be enhanced by any local or systemic treatment. Incision increases the size of the primary ulcer and prolongs its healing. Exacerbation of the general systemic symptoms frequently follows this procedure. Suppurating nodules and glands should be adequately incised and drained only after suppuration is well advanced. Excision of the broken-down glands at this stage, followed by closure of the wound without drainage, is satisfactory. Antiseptics have little or no specific action on primary lesions in the conjunctiva. Hot applications and frequent lavage with warm physiologic solution of sodium chloride are perhaps the most satisfactory treatment.

Foshay [38] recently described the development of an apparently potent goat antiserum for the treatment of tularemia. The intravenous injection of about 10 cc. of this "antitularense" serum on two successive days resulted in an abrupt cessation of fever, malaise, chills, sweats, arthralgia and myalgia, within forty-eight hours after the second injection. There also occurred a rapid reduction in the volume of the involved lymph nodes to an average of one-half their former diameters.

SUMMARY

In addition to a short review of the literature, the characteristic clinical features in 123 cases of tularemia are presented, together with observations at autopsy in 1 case.

37. Foshay, L.: Prophylactic Vaccination Against Tularemia, Am. J. Clin. Path. **2**:7 (Jan.) 1932.

38. Foshay, L.: Serum Treatment of Tularemia, J. A. M. A. **98**:552 (Feb. 13) 1932.

A new classification is presented. Sixty-nine cases occurred in males and 54 in females. One hundred and eight were of the primary cutaneous type, 6 were of the primary ophthalmic type and 9 were of the cryptogenetic type of the disease.

The average incubation period, definitely determined in 58 cases, was four and one-half days.

Sixteen cases presented pulmonary involvement. Primary and secondary pulmonic tularemia are discussed. The breast was involved in 2 cases. Thrombi in the veins were noted in 1 case. Pleurisy was a complication in 6 cases. Abdominal symptoms were prominent in 5 cases. Peritonitis was present in 1 instance. Delirium was a prominent feature in 6 cases. Acute mania complicated 1 case. In 1 case of the primary ophthalmic type optic atrophy occurred, with loss of vision in the affected eye. A purulent dacryocystitis complicated 1 case. Decided splenomegaly with perisplenitis was present in 5 instances. Osteomyelitis was observed once. Cervical adenitis as the only external evidence of the disease was observed in 4 cases. Subcutaneous nodules occurred in 28 instances. A cutaneous eruption was present in 23 cases (18.7 per cent).

There were 5 deaths, indicating a mortality of 4 per cent in this series.

Other pertinent facts pertaining to the history, epidemiology, pathology, diagnosis and treatment are also discussed.

THE SECOND POSITIVE WAVE OF THE Q R S COMPLEX

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AND
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BROOKLYN

Great progress has taken place in the interpretation of electrocardiograms since their introduction. The evolution of the understanding of the significance of the Q R S complex, the R T and S T segments and the T wave has undergone many rapid strides, particularly during recent years, so that the recognition of pathologic variations from the usual normal appearance has become of considerable importance in detecting myocardial damage and abnormalities of the site of impulse production and of conduction and in the localization of cardiac infarction. Detailed attention to the description of the form and contour of the waves has yielded considerable information.

VARIATION

The variation to be described involves the terminal portion of the S wave in lead III.

Of approximately 8,000 serial records, taken from the cardiographic laboratory of the Jewish Hospital of Brooklyn, 320 revealed a positive finding. Of the latter, the data in 50 are herewith reported in a preliminary study, with autopsy records in 3 cases. From a critical analysis of these records it has been repeatedly observed in lead III that following an R wave there is a downwardly directed (negative) S wave, the upward limb of which rises to a variable distance above the iso-electric line in a sharp peak or summit and then descends with varying rapidity and a downward convexity to the iso-electric line, forming thereby a separate and distinct positive wave (fig. 1). This wave may be sharp, pointed, slightly slurred or rounded at its apex; the catacrotic limb may be thickened or feathered. The height to which this wave mounts is variable, and at times may exceed the height of the preceding R wave in the same complex by as much as 5 mm. The contour of the descent of the wave is likewise variable; it may be a sharp and straight declivity merging at once with the so-called S T segment, or, as mentioned previously, it may descend gradually to the iso-electric line in a curving manner with a downward convexity. In its descent, the

From the Cardiographic Laboratory of the Jewish Hospital of Brooklyn.

trough of the wave may occasionally reach a level of from 0.5 to 1 mm. above or below the iso-electric line; rarely, there may be a respiratory variation in its amplitude. Left axis deviation is found in each case. A Q wave, in the ordinary sense, is not present. The nature of the S T segment or the height and direction of the T wave which follows bear no relationship to the wave described.

CRITERIA

We have formulated tentatively the following criteria for the identification of this wave:

1. On standardization, there must be no overshooting (1 cm. current equivalent to 1 millivolt).

2. R_3 must be a distinctly positive deflection above the iso-electric line.

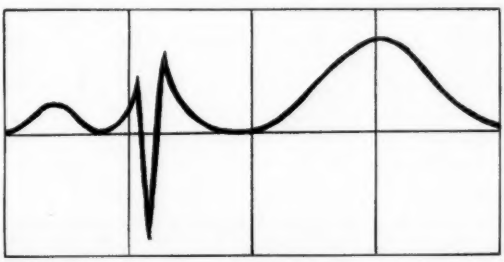

Fig. 1.—Diagram of the second positive wave of the Q R S complex of lead III, as described in the text.

3. R_3 is followed by S_3 of varying amplitude.

4. The upward stroke of S_3 rises above the iso-electric line in a positive peak or summit, as described, and then descends to the iso-electric level.

5. Respiratory and frequency variations in the third lead are excepted.

ANALYSIS OF CASES

The wave described appeared in 320 (4 per cent) of 8,000 records examined. A brief recapitulation of the data in the 50 cases studied is given in the table, with a description of the pertinent electrocardiographic features of the main complex. Briefly summarized, it will be seen:

1. Twenty-eight (56 per cent) cases occurred in males, the average age being 49.1 years. The youngest male patient (case 34), a boy with acute glomerular nephritis of twelve weeks' duration, was 14 years of

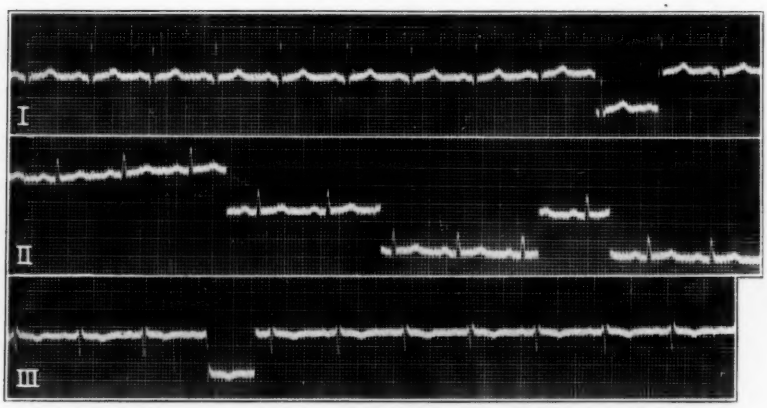

Fig. 2 (case 4).—Electrocardiogram showing regular sinus rhythm; ventricular rate, 75; T_1, very sharply inverted; small main deflections, in lead II, slurred; P R interval in lead II, 0.16 second; T_3, high voltage and sharply pointed; S_3, main deflection, with changes in the height of the S_3 with respiration. Impression: severe myocardial damage and left axis deviation. Diagnosis: diabetes mellitus and coronary thrombosis.

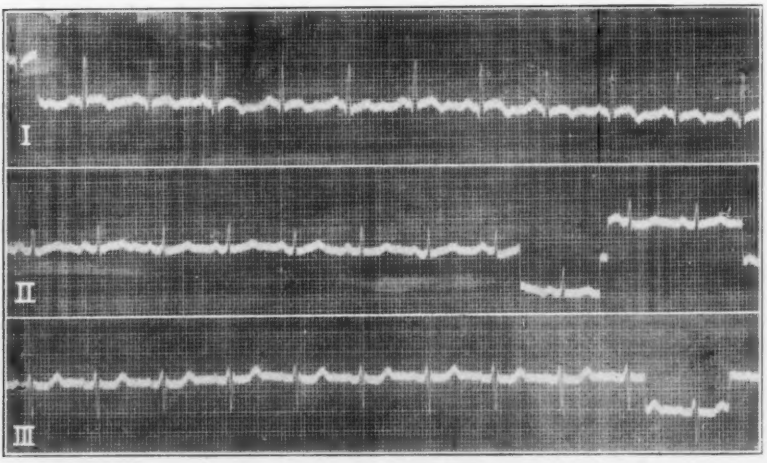

Fig. 3 (case 7).—Electrocardiogram showing left axis deviation; regular sinus rhythm; average ventricular rate, 90; T_1, sharply inverted; P R interval in lead II, 0.16 second; T wave, low voltage; R T interval, depressed below the isoelectric line; S, main deflection. Impression: left axis deviation and myocardial damage. Diagnosis: carcinomatous transformation of a gastric ulcer with metastasis, myocardial fibrosis, aortic sclerosis, coronary thrombosis and sclerosis.

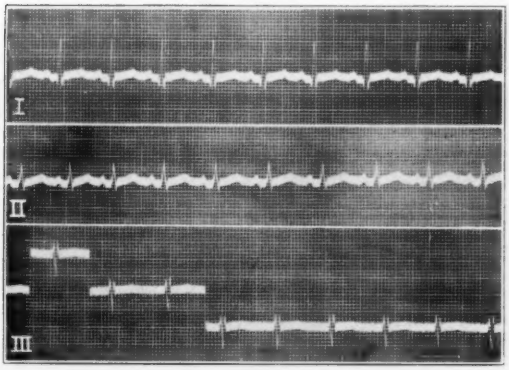

Fig. 4 (case 8).—Electrocardiogram showing regular sinus rhythm; ventricular rate, 100; T wave in lead I, low voltage; poor R T transition in lead II; P R interval in lead II, 0.16 second; slurring of all main deflections; S_3 main deflection in lead II. Impression: myocardial disease and left axis deviation. Diagnosis: rheumatic sepsis, endocarditis, myocarditis, pericarditis, effusion and pneumonia.

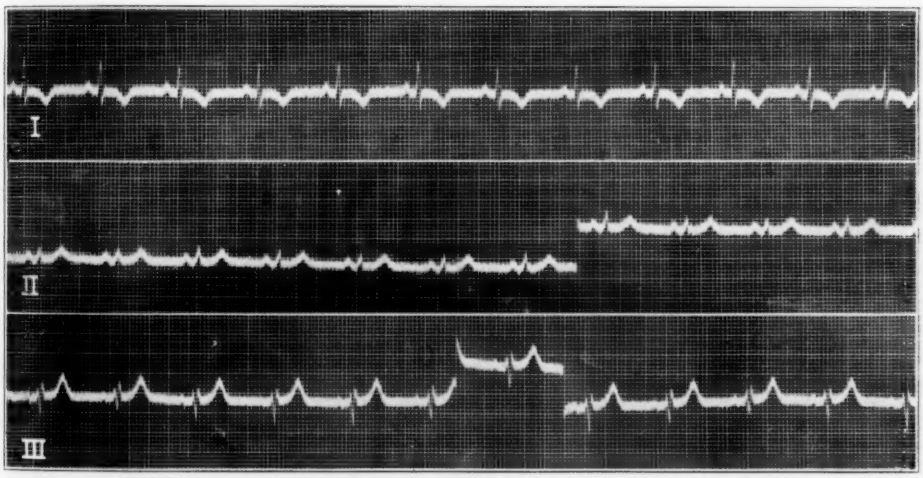

Fig. 5 (case 9).—Electrocardiogram showing left ventricular predominance; T_3, inverted. Diagnosis: acute rheumatic fever and tonsillitis.

age; the oldest (case 37), a man with generalized arteriosclerosis and chronic myocarditis, was 70 years of age.

2. Twenty-two cases occurred in females (44 per cent), the average age being 45.6 years. The youngest patient in this group (case 6), a

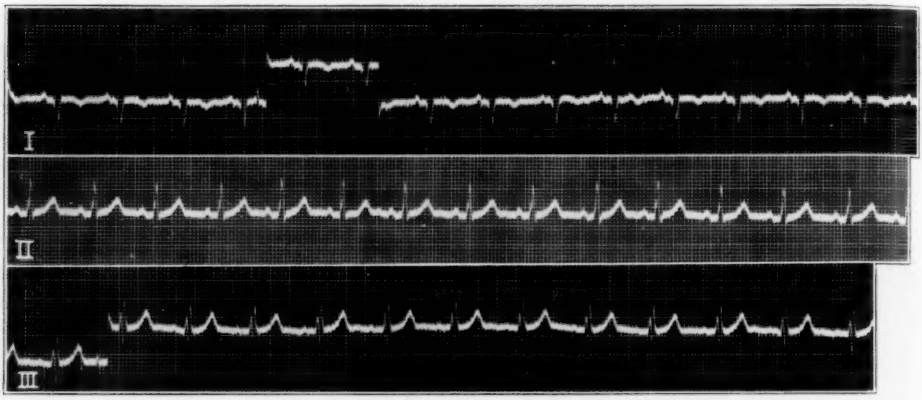

Fig. 6 (case 11).—Electrocardiogram showing regular sinus rhythm; ventricular rate, 85; T_3, inverted; P R interval in lead II, 0.16 second; slurring of main deflection, S_3. Impression: left axis deviation and definite myocardial damage. Diagnosis: coronary closure, fibrinous pericarditis and thrombophlebitis of the leg.

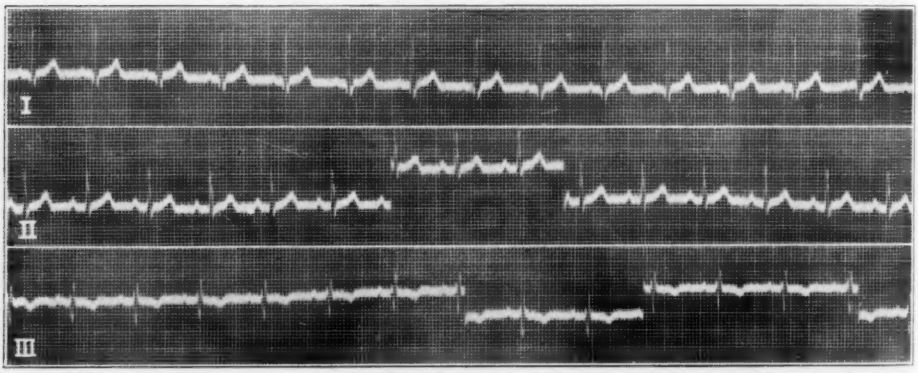

Fig. 7 (case 20).—Electrocardiogram showing ventricular rate, 79; lead I, normal; main complexes, slurred; S_3, deep; T_3, inverted; left ventricular predominance. Diagnosis: acute infectious polyarthritis and general arteriosclerosis.

girl with chronic rheumatic infection six years before admission, complicated by lobar pneumonia and migrating polyarthritis and pericarditis, was 17 years of age; two years before admission there had

been a recurrence in the form of pleurisy, and one year before admission, a recurrence in the form of rheumatic sepsis. The oldest patient in this group (case 31), a woman with generalized arteriosclerosis, coronary and cerebral vascular sclerosis and hypertension, was 70 years of age.

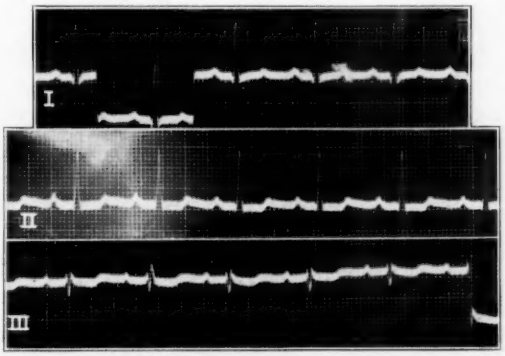

Fig. 8 (case 23).—Electrocardiogram showing ventricular rate, 88 and regular sinus rhythm. Lead I: P, up and widened; P R interval, 0.2 second; R, up and slightly slurred; R T, normal, and T, up. Lead II: P, up; P R interval, 0.22 second; R, up, and ascending limb of R somewhat slurred; R T, normal; T, diphasic. Lead III: P, up; P R interval 0.22 second; S, main deflection and slurred; T, inverted. Conclusion: partial heart block. The slurring of the R waves and the diphasic T waves speak for some myocardial involvement even if the patient had been given digitalis. Diagnosis: hypertension, recurrent rheumatic fever, chronic valvular disease and pericarditis.

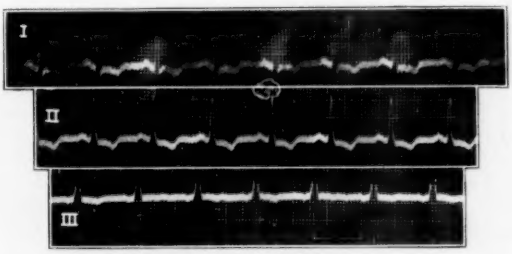

Fig. 9 (case 45).—Electrocardiogram showing ventricular rate, 100. Lead I: P, upright; P R interval, normal; R, slurred; S T, depressed; T, inverted. Lead II: P, upright, high and widened; P R interval, normal; R S, diphasic and slurred; T, upright. Lead III: P, upright, high and widened; P R interval, normal; S, deep and slurred; S T, and T, normal. Conclusion: myocardial damage, auricular hypertrophy and left ventricular predominance. Diagnosis: malignant disease of the lung and chronic rheumatic heart disease.

Data on Fifty Cases, Including Electrocardiographic Features

Case	Age	Sex	Clinical Features	Duration	Clinical Diagnosis	Rate	P	P R	Q R S Amplitude	Q R S Interval	Height of R_2	R_2 T Interval	Direction of T Wave
1	32	F	Decompensation; pain; dyspnea; cough; recurrent rheumatic attacks	Since age of 10 years	Chronic rheumatic valvular disease with effusion	105	Up 1 mm.	0.16	4 mm.	0.08	2.5 mm.	0.12	Up 5 mm.
2	33	F	Pain; swelling; disability of the hand General aches and pains, migratory to joints; sweats preceding pains; dyspnea	4 days 3 weeks	Acute rheumatic fever; polyarthritis	130	Up 5 mm.	0.12	6 mm.	0.06	2 mm.	0.10	Down 2 mm.
3	47	M	Hematuria..... Hemiplegia..... Headache.....	2 weeks 1 day Many years	Malignant hypertension; general arteriosclerosis; nephrosclerosis; hematuria	107	Up 1 mm.	0.14	3.5 mm.	0.06	1 mm.	0.12	Up 1 mm.
4	55	M	Diabetes..... Dyspnea and precordial pain... Sudden attack.....	1 year 8 months 5 days ago	Diabetes mellitus; coronary thrombosis	75	Diphasic	0.12	7 mm.	0.07	3 mm.	0.08	Up 7 mm. sharp
5	55	F	Recurrent rheumatic fever..... Cold; sore throat; arthritis; fugacious pains	Since age of 25 years 4 weeks	Recurrent arthritis of chronic articular rheumatic fever; chronic rheumatic valvular endocarditis; osteo-arthritis	75	Down 1 mm.	0.12	6 mm.	0.06	1.5 mm.	0.24	Down 1 mm.
6	17	F	Grip..... Recurrent attacks of painful joints, fever and sore throat; nephritis, pneumonia and pleurisy Sepsis.....	6 years ago 2 years ago 1 year ago	Chronic rheumatic infection; lobar pneumonia; migrating polyarthritis; old pericarditis	100	Up 1 mm.	0.14	8 mm.	0.04	2.5 mm.	0.14	Down 1 mm.
7	57	M	Dyspnea; substernal pain and oppression; weakness Right-sided pain and loss of 12 pounds (5.4 Kg.)	3 months 3 weeks	Carcinomatous transformation of gastric ulcer with metastasis; myofibrosis; aortic sclerosis; coronary thrombosis and sclerosis	90	Up 1 mm.	0.12	8 mm.	0.08	1.5 mm.	0.12	Up 3.5 mm.
8	24	F	Pains in joints and fever; sore throat and rash	5 days	Rheumatic sepsis; endocarditis; myocarditis; pericarditis; effusion; pneumonia	100	Up 2 mm.	0.12	8 mm.	0.06	3.5 mm.	0.14	Up 5 mm.
9	32	M	Multiple pains and swelling in joints Recurrence of same symptoms plus chill, headache and sore throat	2½ years ago 1 week	Acute rheumatic fever; chronic tonsillitis	75	Iso-electric	0.12	5 mm.	0.06	2.5 mm.	0.18	Down 1 mm.

10	41	M	Scarlet fever as a child; pyrosis at night, helped with sodium bicarbonate Epigastric pressure Substernal pain on walking	5 years 3 months 3 weeks	Coronary sclerosis; angina pectoris; ulcer ?	68	Up 0.5 mm.	0.16	5 mm.	0.06	2.0 mm.	0.18	Up 2 mm.
11	42	M	Weakness; sudden vertigo and pain in calf muscles	7 days	Coronary closure; fibrinous pericarditis; thrombo-phlebitis of leg	85	Up 0.5 mm.	0.14	5 mm.	0.10	7 mm.	0.08	Up 5 mm. sharp
12	40	M	Jaundice; clay stools; dark urine; systolic murmur at apex; throbbing	6 weeks	Acute catarrhal duodenitis	83	Up 1 mm.	0.12	4 mm.	0.08	3 mm.	0.14	Down 0.5 mm.
13	30	M	Headache Failing vision Renal stone passed	2 years 2 weeks 15 years ago	Albuminuric retinitis; essential hypertension; acute capillary fibrosis; uremia; myocarditic failure	90	Up 0.5 mm.	0.16	9 mm.	0.06	3 mm.	0.14	Down 2.5 mm.
14	30	F	Postpartum sepsis Decompensation attacks Polycyclic rheumatic attacks	7 years 7 years 2 weeks	Chronic rheumatic valvular disease; rheumatic polyarthritis	100	Up 2 mm.	0.16	5 mm.	0.06	2 mm.	0.12	Down 0.5 mm.
15	60	M	Pain in lower right quadrant Dysuria Loss of 10 pounds (4.5 Kg.) Boil on buttocks	3 weeks 3 weeks 3 weeks 4 weeks	Perirectal adenitis; abdominal adenitis	107	Up 2 mm.	0.14	3 mm.	0.08	2.5 mm.	0.16	Up 1 mm.
16	67	F	Inability to walk at times Bewildered feeling Weakness, headache, swelling of ankles and lower lids; dyspnea	1 year 1 year 8 months	General arteriosclerosis; cerebral arteriosclerosis; auricular fibrillation; myocardial fibrosis; cardiac decompensation	150	Up 1 mm.	0.14	2 mm.	0.04	3 mm.	0.14	Down 0.5 mm.
17	40	M	Swelling of left femur; pain in left hip joint; cyanosis; presystolic mitral murmur	.....	Mitral disease with decompensation; dyspnitarism; coronary sclerosis	100	Up 0.5 mm.	0.16	3 mm.	0.04	2 mm.	....	Iso-electric
18	67	M	Polydipsia and polyphagia Vertigo; headache; loss of memory Constipation and bitter mouth Weakness Sudden cold, painful feet	10 years 16 months 1 year 8 months 4 weeks	Diabetes mellitus; essential hypertension; general arteriosclerosis of lower extremities; cerebral arteriosclerosis; myocardial fibrosis	88	Up 1 mm.	0.16	7 mm.	0.04	2 mm.	0.18	Down 1 mm.
19	55	F	Headache; asthenia Dyspnea Edema of ankle Varicose veins; pruritus vulvae	10 years 3 years 3 years 3 months	Hypertension; arteriosclerosis	105	Iso-electric	....	6 mm.	0.06	2 mm.	0.18	Down 2 mm.
20	47	M	Rheumatism in left shoulder Rheumatism in ankles, multiple joints and knees	10 years 6 weeks	Acute infectious polyarthritis; general arteriosclerosis	80	Up 2 mm.	0.16	6 mm.	0.08	6 mm.	0.14	Down 3 mm.
21	50	F	Precordial pain Dyspnea and palpitation Weakness and vertigo Grip	3 months 10 years 4 years ago 8 months ago	Menopause syndrome; angina pectoris	100	Iso-electric	....	7 mm.	0.06	3.5 mm.	0.14	Down 1 mm.

Data on Fifty Cases, Including Electrocardiographic Features—Continued

Case	Age	Sex	Clinical Features	Duration	Clinical Diagnosis	Rate	P	P R	Q R S Amplitude	Q R S Interval	Height of R_2	R_2 T Interval	Direction of T Wave
22	63	F	Epigastric pain after meals Dyspnea on exertion; precordial oppression and palpitation Edema Dyspnea on exertion	6 weeks 6 weeks 7 years 9 years	General arteriosclerosis; coronary sclerosis; myocardial fibrosis; dyspituitarism; chronic cholecystitis	80	Up 1 mm.	0.16	3.5 mm.	0.08	2 mm.	0.14	Up 1 mm.
23	33	F	Dyspnea and paroxysmal nocturnal dyspnea and palpitation Precordial oppression and heaviness	1 year Past year	Hypertension; recurrent rheumatic fever; chronic valvular disease; pericarditis; rheumatic pericarditis	88	Up 2 mm.	0.22	3.5 mm.	0.04	4 mm.	0.12	Down 1 mm.
24	45	F	Epigastric pain Cardiac disease Recurrent attacks of orthopnea and dyspnea Same symptoms Diabetes	1 month 6 years 3 months 3 weeks 4 years	Diabetes mellitus; acidosis; postoperative adhesions; neurasthenia; chronic cholecystitis	100	Up 0.5 mm.	0.20	5 mm.	0.04	1.5 mm.	0.14	Down 0.5 mm.
25	52	M	Oppression in chest, repeated several times, with weakness	4 days	General arteriosclerosis; coronary sclerosis; chronic bronchitis and emphysema	70	Up 1.5 mm.	0.18	2 mm.	0.08	1.5 mm.	0.16	Up 1 mm.
26	59	M	Orthopnea and precordial choking Symptoms recurred Precordial pain and pressure	5 years 6 days 3 years	Paroxysmal ventricular tachycardia; coronary sclerosis; chronic myocarditis	75	Up 1.5 mm.	0.20	6 mm.	0.06	1.5 mm.	0.16	Up 1.5 mm.
27	60	F	Pain in right upper quadrant Precordial pain and choking Frontal headache and vertigo	3 months 1 month 2 years	Generalized arteriosclerosis; cardiac arteriosclerosis; coronary sclerosis	88	Diphasic 1 mm.	0.16	3 mm.	0.04	2 mm.	0.16	Down 1 mm.
28	58	M	Nausea; headache; vertigo; weak legs Similar attack Gastro-intestinal symptoms	18 years 4 months ago 4 months	Generalized arteriosclerosis; neurasthenia; chronic constipation	100	Up 0.5 mm.	0.16	5 mm.	0.12	2.5 mm.	0.20	Up 1.5 mm.
29	53	F	Epigastric pain Vomiting Hemoptysis Headache; spots; vertigo; blurred vision Weakness increased Pain in left lower quadrant	2 weeks 4 hours 22 years ago 1 year 1 year 2 weeks	Pyelocystitis; ureteral calculus; chronic myocarditis	125	Up 1 mm.	0.14	7 mm.	0.06	1 mm.	0.10	Up 2.5 mm. sharp

30	55	M	Attacks of precordial pain, distress and dyspnea Rheumatic fever, 2 attacks..... Acute tonsillitis with pains in the joints	5 months 12 yrs., 9 yrs. 3 weeks	Acute tonsillitis; coronary sclerosis	100	Up 1 mm.	0.16	5 mm.	0.08	3.5 mm.	0.16	Down 1 mm.
31	70	F	Drowsiness; asthenia; somnolence; anorexia Increasing weakness..... Hypertension; poor memory...	5 weeks 3 weeks 3 years	Hypertension; cerebral vascular disease; coronary sclerosis; general arteriosclerosis	80	Up 0.5 mm.	0.20	4 mm.	0.04	2 mm.	....	Iso-electric
32	55	M	Precordial pains and distress five times a day; three times a night Regurgitation of food.....	6 months 15 years	Chronic cholecystitis; coronary sclerosis	65	Up 0.5 mm.	0.14	3 mm.	0.04	2 mm.	0.18	Up 2.5 mm.
33	59	M	Intermittent headache; blood pressure, 210/108	5 weeks	Hypertension; cardiac and coronary sclerosis; vascular crises ?	75	Down 1 mm.	0.14	6 mm.	0.06	1.5 mm.	0.14	Up 1 mm.
34	14	M	Swelling of face and left ankle every morning; gone by night	12 weeks	Acute glomerular nephritis	115	Down 1.5 mm.	0.12	5 mm.	0.04	2 mm.	0.16	Down 1.5 mm.
35	54	M	Pain in the chest and back..... Weakness..... Loss of weight.....	3 months 10 months 4 months	Multiple myelomas	115	Up 0.5 mm.	0.14	3 mm.	0.06	4.5 mm.	0.18	Up 1 mm.
36	59	M	Precordial pain..... Reported attacks on exertion.. Dyspnea on exertion.....	6 weeks 6 weeks 6 weeks	Hypertension; disease of the coronary artery	98	Down 1 mm.	0.20	5 mm.	0.06	1.5 mm.	0.12	Up 2 mm.
37	70	M	Nocturnal frequency; urgency; hematuria	1 year	General arteriosclerosis; chronic myocarditis; chronic cystitis; adenomatous prostate	100	Auricular fibrillation	....	5 mm.	0.04	2 mm.	0.14	Down 1.5 mm.
38	32	F	High blood pressure..... Frequent headaches..... Palpitation..... Vertigo; sudden earache..... Headache; vertigo; epigastric and precordial pain, getting worse, radiating to left arm and upper part of chest	10 years 1 year 6 weeks 3 mos., 3 wks. 2 days	Essential hypertension; right hydronephrosis; essential hypertension; cardiac hypertrophy; coronary thrombosis; chronic diffuse nephritis	136	Up 1.5 mm.	0.18	6 mm.	0.06	3.5 mm.	0.12	Down 1 mm.
39	36	M	Fugacious pains and fever..... Weakness preceded by grip, fever and sore throat	6 weeks 6 weeks	Acute rheumatic fever; resolved pneumonia; infectious polyarthritis	80	Up 1.5 mm.	0.14	4 mm.	0.08	4.5 mm.	0.18	Diphasic
40	64	M	Exertional dyspnea..... Cough.....	1 month 3 months	Auricular fibrillation; general arteriosclerosis hypertension; cardiac hypertrophy and dilatation	100	.....	....	5 mm.	0.12	3.5 mm.	0.14	Down 1.5 mm.
41	32	F	Parturition; accidental separation of placenta	Cesarean section	Hypertension; chronic nephritis; accidental separation of placenta	115	Up 1.5 mm.	0.14	5 mm.	0.08	2.5 mm.	0.12	Up 0.5 mm.
42	45	F	Twirling in head; vertigo; shakiness, getting gradually worse	3 years ago	Dysendocrinism; hypothyroidism	120	Up 1 mm.	0.18	4 mm.	0.06	2.5 mm.	0.12	Down 1.5 mm.

Data on Fifty Cases, Including Electrocardiographic Features—Continued

Case	Age	Sex	Clinical Features	Duration	Clinical Diagnosis	Rate	P	P R	Q R S Amplitude	Q R S Interval	Height of R_2	R_2-T Interval	Direction of T Wave
43	45	M	Abdominal pain Pain in right shoulder Pain in left shoulder, radiating down to arm and fingers many times	1 week 3 months 6 weeks	Acute suppurative cholecystitis; acute hepatitis; angina pectoris	100	Up 2 mm.	0.16	6 mm.	0.06	3 mm.	0.20	Diphasic
44	46	F	Pain in joints and sore throat Rheumatic polyarthritis Recurrence of same symptoms.	3 weeks At 15 years At 24 years	Acute and rheumatic polyarthritis; rheumatic heart disease; mitral regurgitation	84	Down 2 mm.	0.16	3 mm.	0.04	3 mm.	0.16	Down 2.5 mm.
45	52	M	Hemoptysis Weakness Rheumatic fever Marked dyspnea	9 months 2 months 1914 9 months	Malignant disease of the lung; chronic rheumatic heart disease	100	Down 1 mm.	0.12	12 mm.	0.10	4 mm.	0.16	Down 1 mm.
46	60	F	.....	.....	Chronic glomerular nephritis; general arteriosclerosis, hypertension; cardiac hypertrophy and dilatation; coronary sclerosis; myocardial fibrosis; general anasarca	88	Down 0.25 mm.	0.12	4 mm.	0.04	1.5 mm.	0.18	Up 0.5 mm.
47	19	M	Fugacious arthritis Slight exertional dyspnea Epistaxis at long intervals	5 years 5 years 2 years	Gaucher's splenomegaly; osteo-arthritis	100	Diphasic 0.5 mm.	0.12	8 mm.	0.04	3 mm.	0.12	Down 3 mm. sharp
48	57	F	Heaviness and abdominal distention with belching after meals Headache Edema of ankle Precordial pain and sticking on exertion	2 years 1 year 1 year 1 year	Arteriosclerosis; hypertension; myocardial degeneration and insufficiency	65	Up 1 mm.	0.16	9 mm.	0.12	3.5 mm.	0.16	Down 2 mm.
49	36	M	Sore throat; pain in muscles and joints Exertional dyspnea; sticking exertional precordial pain; epistaxis; night sweats	6 days Many years	Recurrent rheumatic fever; subacute arthritis; coronary sclerosis; angina pectoris; coronary arteritis	100	Up 1 mm.	0.16	3.5 mm.	0.06	3.5 mm.	0.10	Up 3 mm.
50	45	F	Jaundice Precordial pain Numbness Precordial pain; palpitation and edema	16 years ago 1 week ago 1 day ago 1 year	Chronic cholecystitis; chronic myocardial insufficiency	84	Up 1 mm.	0.12	5 mm.	0.06	1.5 mm.	0.20	Down 1 mm.

3. In 86 per cent, there was clinical evidence of cardiac disease. Of the remaining 7 patients (14 per cent), 5, without symptoms, were between the ages of 40 and 54 years, an age group in which cardiovascular diseases are usually present. The 2 remaining patients were

Fig. 10 (case 47).—Electrocardiogram showing ventricular rate, 100. Lead I: P, upright; P R interval, normal; R, S T and T, normal. Lead II: P, normal; P R interval, normal; R, S T and T, normal. Lead III: P, diphasic; S, deep; T, sharply inverted. Conclusion: left ventricular predominance; sharp inversion of T_3. Diagnosis: Gaucher's splenomegaly and osteo-arthritis.

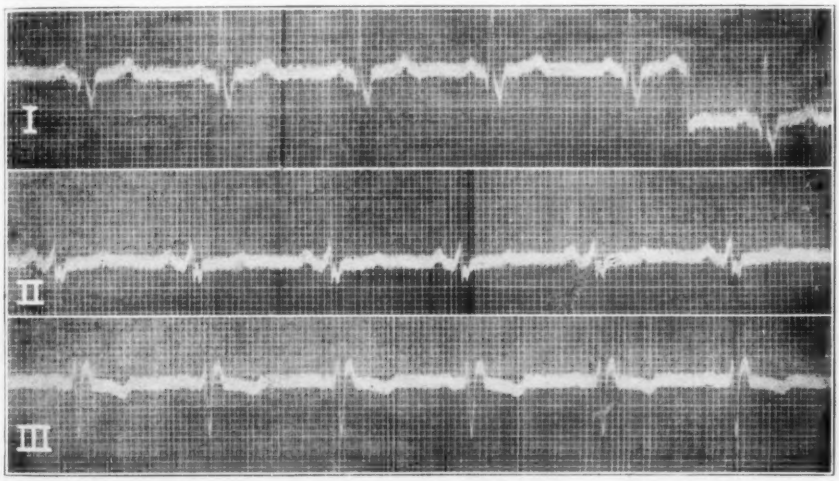

Fig. 11 (case 48).—Electrocardiogram showing ventricular rate, 65, and regular sinus rhythm. Lead I: P, up; P R interval, 0.16 second; R, up and somewhat slurred; widening of the Q R S; S T, normal; T, up. Lead II: P, up; P R interval, 0.16 second; R, low and slurred; T, up and very low, almost iso-electric. Lead III: P, diphasic; P R interval, 0.12 second; S, main deflection and slurred; S T, transition, poor; T, inverted. Conclusion: left ventricular predominance and myocardial involvement. Diagnosis: arteriosclerosis, hypertension and myocardial degeneration and insufficiency.

14 and 19 years of age, respectively. The former suffered from acute glomerular nephritis; the latter from Gaucher's splenomegaly, in which there were cardiac symptoms.

We have diligently searched the literature but have failed to find a previous description of this electrocardiographic alteration. Einthoven, in his original contributions on the electrocardiogram and in his later studies, makes no mention of it,[1] nor did Kraus and Nicolai.[2] Eyster and Meek, in an exhaustive and critical analysis,[3] Carter,[4] Lewis,[5] Master and Pardee,[6] Fahr,[7] Oppenheimer and Rothschild,[8] Levine,[9] Dieuaide[10] and Williams[11] have not referred to this variation in the many papers which they have published, and yet illustrations and numerous electrocardiograms identical with those here described are exhibited.

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SUMMARY

1. In a critical analysis of 8,000 electrocardiograms there is described in 320 (4 per cent) a second positive wave following S_3. Left axis deviation was constantly present.

2. Analysis shows that at least 86 per cent indicated change in the cardiac muscle, and in 14 per cent such changes may have been present.

3. Neither sex nor age seems to account for the presence of the wave, though there was a slight predominance in males.

4. In an extensive review of the literature, no previous description of this electrocardiographic abnormality has been found.

CONCLUSIONS

1. The second positive wave of the Q R S complex is found with great regularity in electrocardiograms made in cases of myocardial disease.

2. It has not been found in a study of the abnormal electrocardiogram.

ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF ACUTE LOBAR PNEUMONIA

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AND
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CHICAGO

Since 1921 when Friedmann [1] reported that artificial pneumothorax was a valuable procedure in the treatment of lobar pneumonia, isolated reports of various observers have been published that substantiate his claims. Recently Lieberman and Leopold [2] reviewed the results of fifty published cases and found a mortality of only 6 per cent. More striking than the low mortality figure is the dramatic symptomatic relief which is consistently produced by this measure. Coghlan [3] reported that with pneumothorax he was able to produce a crisis which simulated a natural crisis. The improvement was maintained by the employment of subsequent refills. Support for these optimistic clinical results is presented by Lieberman and Leopold, who carried out experiments with dogs. Producing lobar pneumonia by the Robertson method, they noted a mortality of 16 per cent in the group treated by pneumothorax and a mortality of 72 per cent in the control group.

The lack of a rational explanation of the beneficial results has caused concern to most of the observers. Coghlan ventured the following explanation: (1) Relief from pain and dyspnea is produced by a separation of the inflamed pleural surfaces; (2) the inflamed lung is placed at rest; (3) toxins are prevented from entering the general circulation, and anoxemia is diminished because the procedure limits the flow of blood through the lung.

Possible dangers were discussed by Coghlan and Lieberman. They agreed that circulatory collapse may be initiated as the result of cardiac and mediastinal displacement. There have been no reports of pleural shock, pyopneumothorax, pulmonary abscess, pulmonary gangrene, pulmonary embolism or septicemia as complications of the treatment.

We have used artificial pneumothorax as a therapeutic measure on twelve patients with lobar pneumonia at Cook County Hospital. The patients were selected from a group of eighteen admitted to the ward during the period of the study. Six patients were excluded for the

From the Cook County Hospital and Northwestern University Medical School.

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following reasons: Two showed bilateral involvement; two had bronchopneumonia; in one there was a suggestion of apical tuberculosis, and one was in a dying state when admitted. The technic was like that described by Coghlan.[3] To exclude bilateral pulmonary involvement and

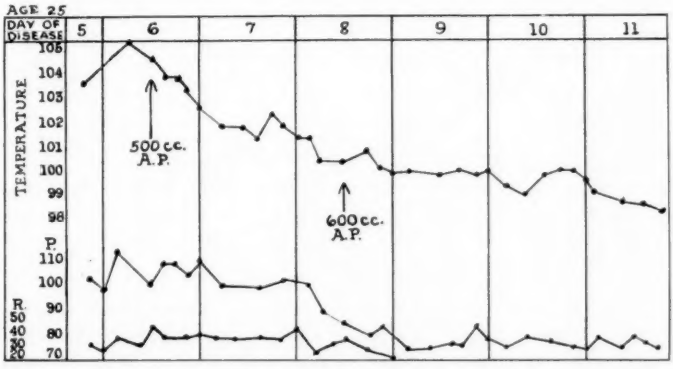

Fig. 1 (case 1).—Pneumonia of all of the lobes of the right lung. There was immediate relief from pain and dyspnea. Sweating was profuse. Recovery was uneventful. *AP* signifies artificial pneumothorax; *R*, respiratory rate; *P*, pulse rate.

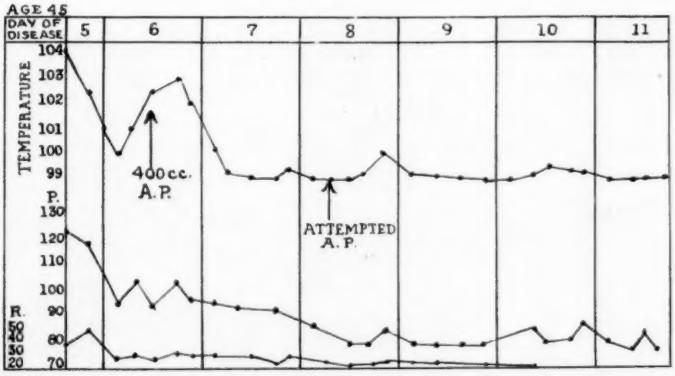

Fig. 2 (case 2).—Pneumonia of the right upper lobe. The leukocyte count was 23,000 on the sixth, and 20,000 on the seventh day of the disease. Spectacular relief from pain, dyspnea and the toxic appearance took place. There was a positive pleural pressure on the second attempt to refill. Recovery was uneventful.

confirm the diagnosis, preliminary roentgen films were made. Within eight hours after pneumothorax and just prior to discharge roentgen films were again made.

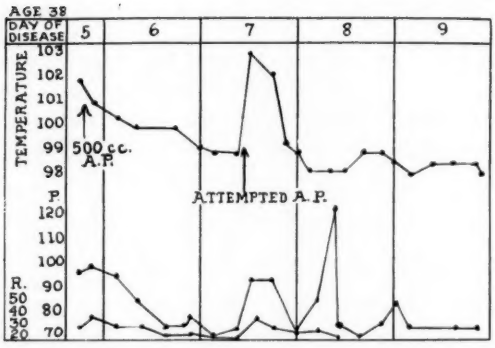

Fig. 3 (case 3).—Pneumonia of the left lower lobe. The leukocyte count was 12,200 on the fifth day and 17,200 on the eighth. The crisis was typical, with complete symptomatic relief. There were no complaints during the rise in fever on the seventh day. Recovery was uneventful.

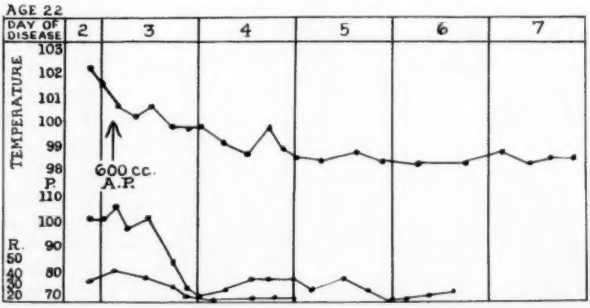

Fig. 4 (case 4).—Pneumonia of the right lower lobe. The leukocyte count was 20,100 on the third day and 17,450 on the fifth. The crisis was spectacular, and the symptomatic relief immediate.

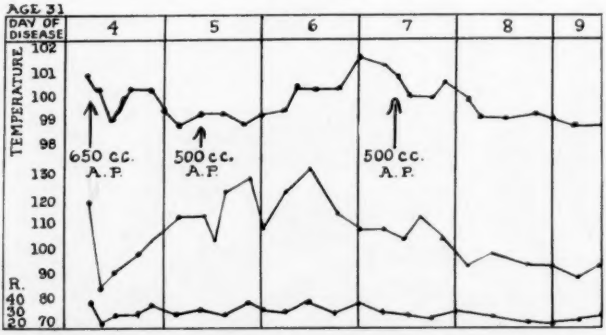

Fig. 5 (case 5).—Pneumonia of the left upper lobe. There were delirium tremens and meningismus. The patient's condition was highly toxic and he perspired profusely after each pneumothorax. Relief from delirium was gradual.

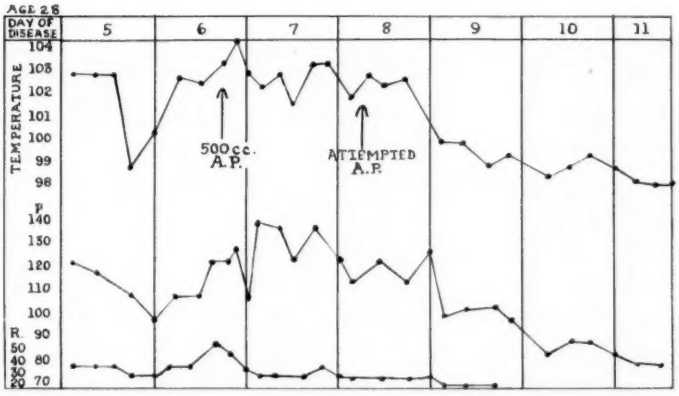

Fig. 6 (case 6).—Pneumonia of all of the lobes of the right lung. The leukocyte count was 27,200 on the sixth day, 24,400 on the eighth day and 25,300 on the ninth day. The patient was profoundly toxic; there were marked pain, severe hiccups and jaundice. Friedländer's bacilli were present in the sputum. The pain and the hiccups were stopped by the pneumothorax. The jaundice persisted until the eleventh day. Recovery was uneventful.

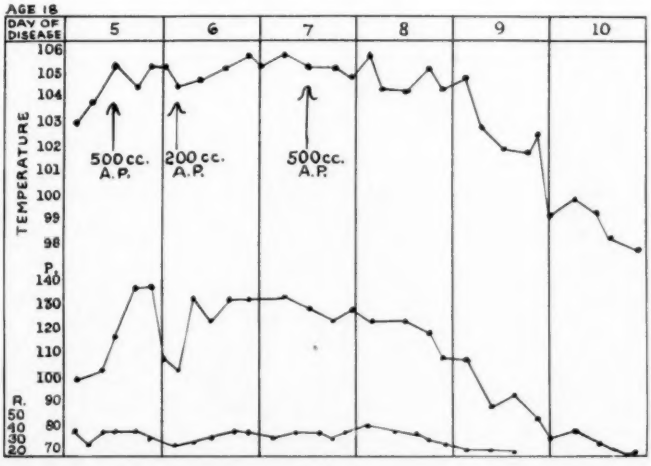

Fig. 7 (case 7).—Pneumonia of the left lower lobe. The leukocyte count was 23,200 on the fifth, 24,000 on the sixth, 26,000 on the seventh and 25,000 on the eighth day. Perspiration was profuse. Relief from pain occurred after the first pneumothorax. Recovery was good.

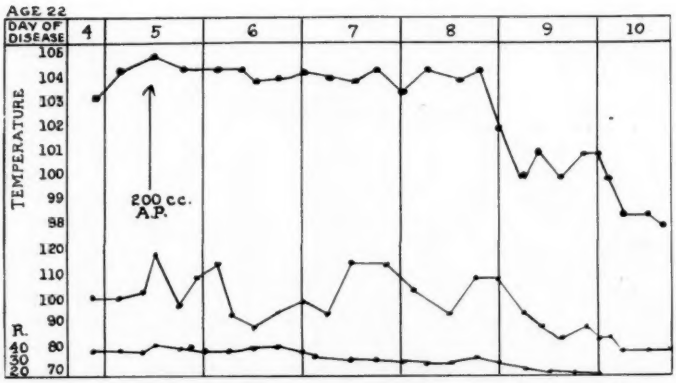

Fig. 8 (case 8).—Lobar pneumonia of all of the lobes of the right lung. The leukocyte count was 15,000 on the fourth day and 13,800 on the seventh. The pneumothorax was limited to 200 cc. of air because the pressure was positive. Slight sweating and relief from pain occurred. Recovery was uneventful.

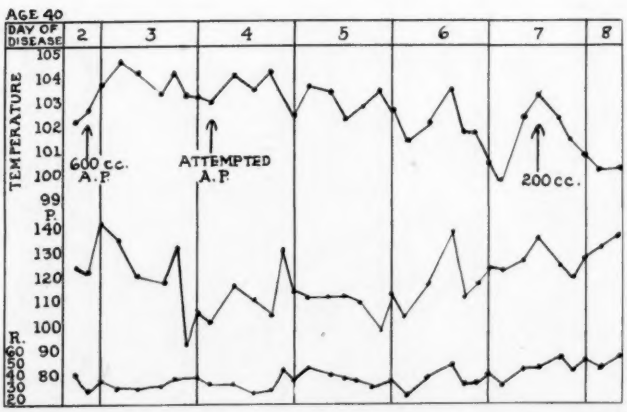

Fig. 9 (case 9).—Pneumonia of the right lower and upper lobes. The first pneumothorax caused perspiration and relief from pain. At the second pneumothorax pleural fluid was encountered. Consolidation of the left upper lobe occurred two days before death, and there was terminal meningismus. Autopsy was performed.

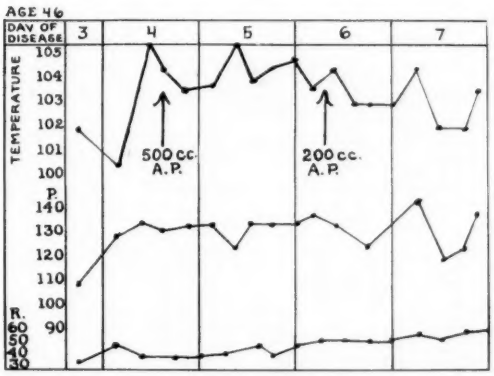

Fig. 10 (case 10).—Pneumonia of the left lower lobe. The leukocyte count was 15,000 on the third day and 22,000 on the sixth. The patient had delirium tremens; he was toxic and dyspneic and presented marked cyanosis. There was no improvement after pneumothorax. Death occurred. Autopsy was not performed.

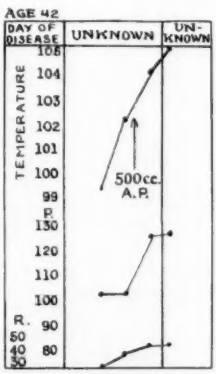

Fig. 11 (case 11).—Pneumonia of the right upper lobe. The patient had delirium tremens; there was deep cyanosis but no sweating. Death occurred. No autopsy was performed.

RESULTS

The results obtained were not so good as those obtained by other investigators. As shown by the charts, four patients (figs. 1 to 4) obtained immediate symptomatic relief that was quickly followed by a lowering of the fever and of the pulse rate; four patients (figs. 5 to 8) obtained symptomatic relief, but there was little or no lowering of the fever or pulse rate, and four patients (figs. 9 to 12) died.

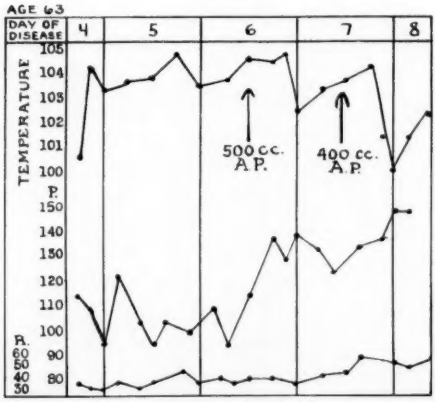

Fig. 12 (case 12).—Pneumonia of all of the lobes of the right lung. The leukocyte count was 12,450 on the fourth day, 6,600 on the sixth day and 6,100 on the seventh day. The patient was an emaciated old man, with marked generalized arteriosclerosis; there was no symptomatic relief. Death occurred. Autopsy was not performed.

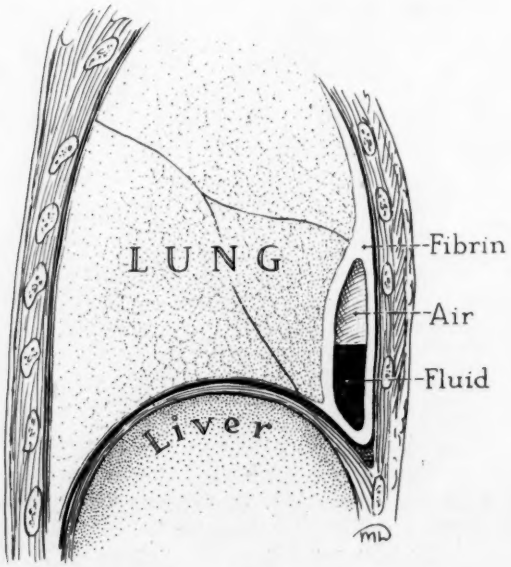

Fig. 13 (case 9).—Drawing illustrating the localized pneumothorax.

REPORT OF FATAL CASES

CASE 9.—A white man, aged 40, with involvement of the upper and lower lobe of the right lung, received 500 cc. of air by artificial pneumothorax on the second day of the disease. A refill on the third day was unsuccessful, and physical examination revealed evidence of pneumothorax on succeeding days, until the seventh day, when 200 cc. of air was again introduced into the pleural cavity. The patient died on the eighth day. Autopsy revealed lobar pneumonia in a stage of gray hepatization in all of the lobes of the right lung and a patch of early pneumonia in the upper lobe of the left lung. An extensive, thick layer of fibrin covered all parts of the right lung, especially anteriorly, and extended over the anterior mediastinum. Anterior and lateral to the right lower lobe in this dense mass of fibrin was a completely walled-off pocket which contained 150 cc. of purulent fluid and a similar quantity of air.

CASE 10.—A colored man, aged 46, chronically alcoholic, was admitted in a state of delirium tremens; he was profoundly dyspneic and cyanotic. Roentgeno-

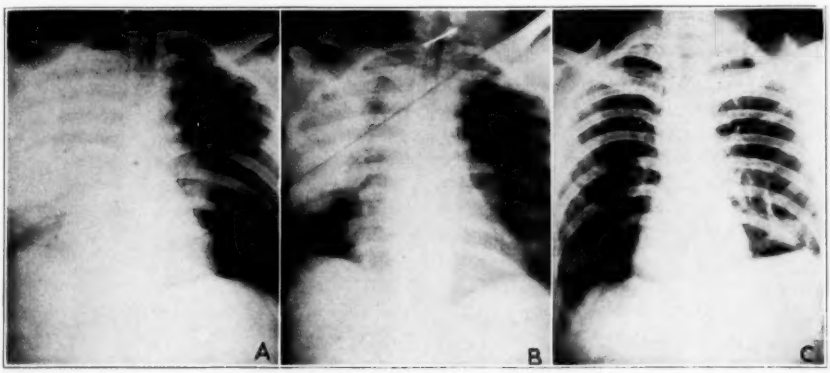

Fig. 14 (case 1).—*A*, Roentgenogram taken before the pneumothorax; *B*, roentgenogram taken four hours after the pneumothorax, and *C*, roentgenogram taken eight days after the crisis, showing no harmful residue.

grams revealed involvement of the left lower lobe. No relief was obtained from artificial pneumothorax on the fourth and sixth days of the disease. The patient died on the seventh day. No autopsy was made.

CASE 11.—A white man, aged 42, was admitted in a state of delirium tremens. He received pneumothorax four hours after admission and died four hours later. The dyspnea, cyanosis and toxic appearance were neither improved nor adversely affected by the pneumothorax.

CASE 12.—An emaciated man, aged 63, with generalized arteriosclerosis, received pneumothorax on the sixth and seventh days of the disease. The preliminary roentgenograms revealed involvement of practically all of the right lung. No symptomatic relief was obtained, and the patient died on the eighth day. Autopsy revealed not only lobar pneumonia involving all of the lobes of the right lung but a large patch of bronchopneumonia in the lower lobe of the left lung. There was no air in the right pleural cavity and only slight fibrinous pleuritis.

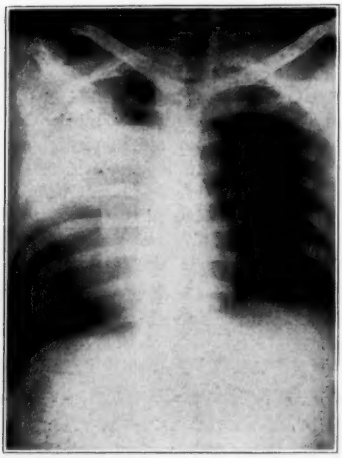

Fig. 15 (case 5).—Roentgenogram taken four hours after the pneumothorax. Note the air around the apex and the base.

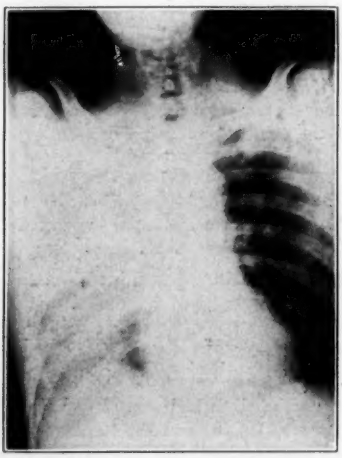

Fig. 16 (case 6).—Roentgenogram taken six hours after the pneumothorax. Note the elevation of the lung above the diaphragm. Relief from hiccup was obtained.

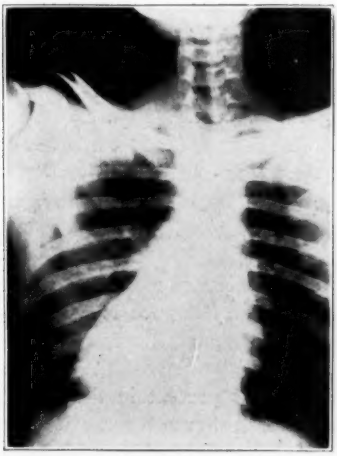

Fig. 17 (case 7).—Roentgenogram showing considerable pulmonary collapse.

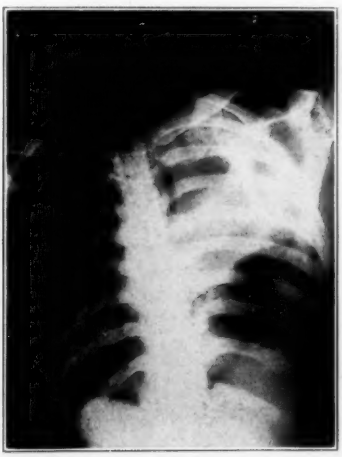

Fig. 18 (case 9.—Roentgenogram taken after the first pneumothorax. The patient died.

ROENTGEN STUDIES

As a precautionary measure to eliminate bilateral involvement no treatment was given until after roentgenograms were made. Films were repeated within from four to twelve hours after the pneumothorax and again prior to discharge from the hospital. The localization of the air and its effect on the lung varied widely. Figure 14 shows reproductions of roentgenograms made of the patient in case 1. A large pocket of air was present around the lower lobe, and a smaller amount outlined the medial border and apex. It is possible that the diffuse distribution of the air and the partial collapsing effect on the lower lobe account for the favorable results in this case. Figure 15 shows air around the apex and the base in case 5, but there was no crisis produced in this case. Figure 16 reveals air around the lower lobe, with separation of the diaphragm and the lung (case 6). Immediate relief from hiccups was a feature in this case. Figure 17 (case 7) reveals more extensive pulmonary collapse than was present in the other cases, and yet the procedure effected no relief from the fever. Figure 18 (case 9) reveals a large quantity of air present following the initial pneumothorax in a patient who subsequently died with the pleural cavity completely obliterated by fibrin.

COMMENT

When one is studying an individual case or a small series of cases of lobar pneumonia, it is difficult to evaluate the effect of any type of treatment. It is particularly difficult to evaluate a crisis-inducing therapeutic measure when it is applied on the fifth day of the disease or later. Such was the case in most of the patients of this series. Even the spectacular results obtained in case 4 on the second day of the disease might properly be thought of as a natural crisis, since crises occasionally develop at this early stage. The effect of artificial pneumothorax on the mortality rate cannot be determined from this series or from previously published reports of cases, because the cases were selected and the severer forms (bilateral) eliminated. In this connection the higher mortality rate experienced in our study properly might be attributed to bad judgment in the selection of patients. Thus our group of patients with fatal cases included an emaciated old man with arteriosclerosis, two alcoholic patients with delirium tremens and a man in whom pneumonia developed later in the opposite lung.

Careful analysis of the fatal cases in this series reveals no proof that pneumothorax aggravated the disease or contributed to the fatal outcome. However, the postmortem observations in one patient (case 9) suggest that marked fibrinous pleuritis and pyopneumothorax may be stimulated by the procedure. The development after artificial pneumothorax of lobar pneumonia of the opposite lung in one patient and bron-

chopneumonia in the opposite lung of another patient also suggests a possible hazard.

In spite of these insinuations of doubt, one cannot escape the fact that immediate relief from pain and dyspnea is a striking effect of artificial pneumothorax in lobar pneumonia. Immediate relief from hiccups was also observed once. Profuse sweating like that seen in a natural crisis was usually produced within a few minutes after the pneumothorax. No consistent effect on the leukocyte count was demonstrated. The widespread distribution of air in the pleural cavity after pneumothorax and the relatively small amount of pulmonary collapse

Lower Limits of Water Pressure Before and After Pneumothorax in Twelve Selected Patients

Case	Date	Lower Limits of Water Pressure Before Pneumothorax	Quantity of Air, Cc.	Lower Limits of Water Pressure After Pneumothorax
1. J. H.	3/ 6	— 5	400	+ 2
2. J. N.	2/21	— 6	500	— 2
	2/26	— 4	600	— 1
3. R. K.	2/16	— 8	600	0
	2/21	— 3	200	+ 4
4. H. G.	1/25	— 2	400	+ 8
	1/27	+ 2	0	....
5. A. D.	2/13	— 6	500	— 2
	2/15	+ 1	0	....
6. G. W.	2/12	— 3	500	0
	2/14	+ 2	0	....
7. M. B.	2/15	— 5	500	0
	2/17	— 4	500	0
8. R. G.	2/14	— 5	600	0
9. J. C.	3/ 7	— 7	650	0
	3/ 8	— 4	500	+ 2
	3/10	— 4	500	— 2
10. R. N.	3/ 6	— 6	500	— 1
	3/ 8	— 3	200	+ 6
11. F. P.	3/12	— 2	200	+ 8
12. O. H.	3/ 5	— 4	500	0
	3/ 6	— 4	400	+ 2

seem to indicate that the symptomatic relief depends on the separation of visceral and parietal pleura and partial immobilization of the lung. No explanation of the sweating phenomenon is indicated.

SUMMARY

Twelve selected patients with acute unilateral lobar pneumonia were treated by artificial pneumothorax. Nine received immediate symptomatic relief from pain and dyspnea. It appeared that the procedure brought on an artificial crisis in four patients. Four (33 per cent) died, and necropsies revealed an early pneumonia in the opposite lung of two patients. A localized pyopneumothorax was present at necropsy near the site of thoracentesis in one patient.

CIRCULATION TIME IN FAILURE OF THE LEFT SIDE OF THE HEART

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Increased attention has been devoted of late to the old clinical concept of left ventricular failure. Excellent surveys have been reported by White [1] and by Weiss and Robb.[2] The clinical manifestations are those resulting from pulmonary engorgement, and include various combinations of the following: exertional dyspnea, cardiac asthma, orthopnea, cyanosis, cough, blood-streaked sputum, physical signs and roentgen evidence of pulmonary engorgement, diminution in vital capacity, pulmonary edema, dilatation of the left ventricle and auricle, accentuation of the pulmonic second sound, the systolic murmur of relative mitral insufficiency, gallop rhythm, fall in arterial pressure and, rarely, alternation of the pulse. On the other hand, engorgement of the systemic veins, swelling of the liver, dependent edema and other manifestations of insufficiency of the right side of the heart are absent.

The characteristic clinical picture of isolated failure of the left side of the heart is encountered only when the functional capacity of the right ventricle is adequate to master the increased resistance in the pulmonary circuit that results from insufficiency of the left side of the heart. The dynamics of the circulation are then so altered that the pressure in the systemic veins is unchanged despite the engorgement of the lesser circulation. The negative characteristic of isolated failure of the left side of the heart, the absence of engorgement of the systemic veins, is readily demonstrated by direct measurement of the pressure in a superficial vein. Unfortunately however, no method is available for measuring in man the blood pressure in any portion of the pulmonary

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1. White, P. D.: Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle, J. A. M. A. **100**:1993 (June 24) 1933.

2. Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and Syndrome of Left Ventricular Failure, J. A. M. A. **100**:1841 (June 10) 1933.

circuit. It is true that marked elevation in pressure in the pulmonary circuit can generally be inferred from the clinical symptoms already enumerated. But there are also many cases in which the clinical evidence of pulmonary engorgement are obscure and lead to diagnostic difficulties. For instance, one is not rarely in doubt whether paroxysmal dyspnea in a middle-aged or elderly person is due to bronchial asthma or results from left ventricular failure in coronary arteriosclerosis (cardiac asthma). Another occasional dilemma is to determine whether dyspnea and thoracic pain indicate mediastinal tumor or are correlated with arteriosclerotic heart disease.

Lacking methods for measurement of the pressure within the pulmonary circuit, other means must be invoked to aid in the recognition of pulmonary engorgement when the usual clinical evidences are obscure. One is the measurement of the circulation time along a pathway which includes the pulmonary circuit. Since the pulmonary engorgement of failure of the left side of the heart is a passive congestion, it would appear a priori that there should be a tendency to a retardation of the blood flow through the lungs, with corresponding prolongation of the circulation time along any pathway which includes the pulmonary circuit. That this is actually the case is indicated by the observation of Blumgart and Weiss [3] and Tarr, Oppenheimer and Sager,[4] who observed prolongation of the circulation time in various diseases marked by the type of circulatory disturbance here termed failure of the left side of the heart.

In the following, we present data on the circulation time and venous pressure in failure of the left side of the heart by methods which are easily carried out and thus facilitate the recognition of failure of the left side of the heart in clinical work, not only in the hospital but also by the practitioner without laboratory facilities.

METHODS

Arm-to-Tongue Circulation Time.—The arm-to-tongue circulation time was measured by the interval elapsing between the injection of gluside into an antecubital vein and the perception of the sweet taste in the tongue (Fishberg, Hitzig and King [5]). By this technic, the arm-to-tongue circulation time in health is between nine and sixteen seconds.

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3. Blumgart, H. L., and Weiss, S.: The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardio-Vascular Disease, J. Clin. Investigation **5**:343, 1928.

4. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933.

5. Fishberg, A. M.: Hitzig, W. M., and King, F. H.: Measurement of Circulation Time with Saccharin, Proc. Soc. Exper. Biol & Med. **30**:651, 1933.

Arm-to-Lung Circulation Time.—This is measured by a method described by Hitzig.[6] Five minims of ether mixed with an equal volume of physiologic solution of sodium chloride is injected into an antecubital vein, and the time elapsing until the ether vapor in the expired air is perceived by the subject and an observer is noted. The interval is a measure of the circulation time between the antecubital vein and the arterial capillaries of the lung, which in health, varies between four and eight seconds.

Venous Pressure.—This was measured in an antecubital vein by a slight modification of the method of Taylor, Thomas and Schleiter.[7] The manometer is an L-shaped tube of glass, to the short limb of which a 19-gage needle is attached. The tube is moistened with a 10 per cent solution of sodium citrate. The arm is supported, so that the vein is at the level of the right auricle. The needle is introduced into the vein. The height to which the blood rises in the vertical limb of the tube indicates the venous pressure. The details of the method were given elsewhere by Fishberg, Hitzig and King.[8] In health, the venous pressure is between 4 and 8 cm. of blood.

CIRCULATION TIME

The arm-to-tongue circulation time is measured along the pathway from a large antecubital vein to the arterial capillaries of the tongue. In table 1 are listed the arm-to-tongue circulation time and the venous pressure of thirty-one patients presenting the clinical picture of severe failure of the left side of the heart, as described previously. It will be noted that the arm-to-tongue circulation time is markedly prolonged in all but the last patient; and even in this one it was above the upper limit of normal on one occasion. The cases listed in the table are representative of our general observation, on over eight hundred patients in whom we have measured the arm-to-tongue circulation time, that the vast majority of persons with well marked symptoms of failure of the left side of the heart have prolonged arm-to-tongue circulation time. Indeed, in some cases the arm-to-tongue circulation time is more than triple the normal time. In order to evaluate the significance of this prolongation, it is necessary to consider individually the component pathways of the circuit traversed by the gluside.

1. The first is the venous pathway from the antecubital vein to the right side of the heart. The fact that the venous pressure is normal indicates that little of the prolongation of the circulation time is attributable to slowing of the blood flow in the large veins, for when heart failure results in stasis in the systemic veins, the pressure in the antecubital vein rises. And the fact that the arterial pressure was not

6. Hitzig, W. M.: Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries. Proc. Soc. Exper. Biol. & Med. **31**:935, 1934.

7. Taylor, F. A.; Thomas, A. B., and Schleiter, H. G.: Direct Method for Estimation of Venous Pressure, Proc. Soc. Exper. Biol. & Med. **27**:867, 1930.

8. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, Arch. Int. Med. **54**:997 (Dec.) 1934.

depressed in most of our patients indicates that diminished vis a tergo can hardly come into play as a cause of slowing of the blood flow in the veins, even though the volume output of the heart is doubtless

TABLE 1.—*Venous Pressure and Arm-to-Tongue Circulation Time in Failure of the Left Side of the Heart*

Diagnosis	Venous Pressure, Cm. of Blood	Arm-to-Tongue Circulation Time, Seconds
Essential hypertension, coronary arteriosclerosis	6	30
Essential hypertension, coronary arteriosclerosis	4	30
After digitalization	5	18.5
Essential hypertension in a malignant phase	7	38
Essential hypertension in a malignant phase	5.5	37
Essential hypertension in a malignant phase	5	30
	5.5	30
Coronary arteriosclerosis with myocardial damage	8	33
After digitalization	5	18
Coronary arteriosclerosis with myocardial damage	3	35
Coronary arteriosclerosis with myocardial damage	7	27
Coronary thrombosis	8	42
	6.5	36
Coronary thrombosis	4.5	32
Coronary thrombosis	3	33.5
Coronary thrombosis	4.5	38
Coronary thrombosis	6	29
	5.5	34
Coronary thrombosis	8.5	40
	8	39
	5.5	42
	7.5	35.75
Coronary thrombosis	3.5	51.75
	6.5	60.5
	7.5	39
Coronary thrombosis	7.5	35.5
Acute glomerulonephritis with pulmonary edema	6	28
Chronic glomerulonephritis	4	30
Syphilitic aortitis, aortic insufficiency	4	37
Syphilitic aortitis, aortic insufficiency	6.5	25.5
Syphilitic aortitis, aortic insufficiency	5.5	26.75
Syphilitic aortitis, aortic insufficiency	7.5	45.5
Syphilitic aortitis, aortic insufficiency	7.5	23.5
Mitral insufficiency and stenosis	6	30
Mitral insufficiency and stenosis	8	34
Mitral insufficiency and stenosis, aortic insufficiency	3	55
Aortic insufficiency, subacute bacterial endocarditis	6.5	30
Old rheumatic disease of aortic, mitral and tricuspid valves, subacute bacterial endocarditis	6.5	23
Heart block of undetermined origin	7.5	48
	6	44
	4.5	38.75
Arteriovenous aneurysm (popliteal) before operation	4	32
24 hours after operative obliteration of fistula	5	13
Hypertensive heart disease: nephritis (?) essential (?)	5	11.25
	8.5	19
	8.5	13.75

diminished in many instances. Theoretical considerations thus indicate that retardation of the blood flow in the large systemic veins is not responsible for the prolongation of the arm-to-tongue circulation time in persons with isolated failure of the left side of the heart. Observations made by the radium C method, described by Blumgart and Weiss,[3] are in accord with these inferences. In patients with syphilitic heart

disease, suffering from what was evidently left ventricular failure, they found relatively little slowing of the blood flow between the antecubital vein and the right side of the heart.

After the first draft of this paper had been completed, we were able to obtain direct evidence that in many instances of failure of the left side of the heart there is no slowing of the blood flow in the large systemic veins. The evidence is afforded by the results of measurements of the arm-to-lung circulation time by the ether method. This method affords a measure of the circulation time from the antecubital vein to the arterial capillaries of the lung. In table 2 are listed the arm-to-tongue (gluside) time, the arm-to-lung (ether) time and the venous pressure of seven patients with the typical and severe picture of isolated failure of the left side of the heart.

TABLE 2.—*Arm-to-Tongue and Arm-to-Lung Circulation Time and Venous Pressure in Failure of the Left Side of the Heart*

Diagnosis	Venous Pressure, Cm. of Blood	Arm-to-Tongue Circulation Time, Seconds	Arm-to-Lung Circulation Time, Seconds
Coronary arteriosclerosis with myocardial damage...	6	30 32	5 5.5
Coronary arteriosclerosis with myocardial damage...	8	33 31	6 5
Hypertensive and arteriosclerotic heart disease.....	5.5	29	6.5
Mitral stenosis and insufficiency, aortic insufficiency..	7	35	6.5
Mitral stenosis and insufficiency.....	5	24	5.75
Mitral stenosis and insufficiency.....	6.5	22 21	7 6.5
Syphilitic aortitis, aortic insufficiency.....	6	23	4.5

In these cases, the arm-to-lung circulation time was within normal limits despite the prolongation of the arm-to-tongue circulation time. This observation shows that in typical failure of the left side of the heart the prolongation of the arm-to-tongue circulation time is due entirely to slowing of the blood flow downstream to the arterial capillaries of the lung. We have also observed cases showing the clinical picture of failure of the left side of the heart in which the ether time as well as the gluside time was prolonged; in such instances, it is to be presumed that there is also some degree of insufficiency of the right side of the heart, although it is not sufficiently pronounced to result in elevation of the pressure in the systemic veins.

2. The second component is the pulmonary pathway from the right to the left side of the heart. The evidence is strong that almost all the prolongation of the arm-to-tongue circulation time observed in patients with failure of the left side of the heart is due to slowing of the blood flow through the lungs. The clinical features of failure of the left side of the heart listed earlier point unequivocally to the stasis of

blood in the pulmonary vessels. The roentgenographic appearance of the pulmonary vessels at the hilus and in the lung fields leaves no doubt that they are distended with blood in marked insufficiency of the left side of the heart. This distention results in an increase in the aggregate cross-section of the pulmonary vascular bed along its entire length. With such an increase in cross-section of the stream bed, a correspondingly decreased velocity of blood flow serves to transport the same volume of blood per minute from the right to the left side of the heart. Further, from the previous observations with the ether method, the conclusion can be drawn that the slowing of the blood flow is almost entirely in that portion of the pulmonary circuit downstream to the arterial capillaries.

3. The third component is the arterial pathway from the left side of the heart to the tongue. The time required to traverse the arterial pathway is doubtless very small in comparison with the total arm-to-tongue circulation time. We do not know how long a time elapses after the gluside has reached the arterial capillaries of the tongue before the taste buds are stimulated, but there seems no reason to believe that the time is prolonged by circulatory failure.

All in all, it appears justified to conclude that in patients with the clinical picture of failure of the left side of the heart and normal venous pressure the prolongation of the arm-to-tongue circulation time is due almost entirely to slowing of the blood flow through that portion of the pulmonary circuit downstream to the arterial capillaries.

It is to be emphasized that we found no strict parallelism between the prolongation of the arm-to-tongue circulation time and the intensity of the dyspnea and other symptoms of failure of the left side of the heart. To a large extent, such discrepancies seem to be attributable to the fact that there is no constant relationship between the pressure in the pulmonary circuit and the velocity of blood flow through it. The experimental investigations of von Basch,[9] Drinker, Peabody and Blumgart [10] and others have shown that an increase in pressure in the pulmonary circuit is an important factor in producing dyspnea, diminution in vital capacity and other symptoms of failure of the left side of the heart. The pressure in the pulmonary circuit is determined not only by the efficiency of the left ventricle and the capacity of the stream bed, but also by the volume of blood pumped into the pulmonary artery by the right side of the heart. The latter is decreased under two circumstances which are important in the present connection.

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9. von Basch, S.: Klinische und experimentelle Untersuchungen, Berlin, A. Hirschwald, 1891, vol. 1, p. 53.

10. Drinker, C. E.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, J. Exper. Med. **35**:77, 1922.

1. The first is the diminution in the venous return to the right side of the heart which occurs in different varieties of shock. The right side of the heart can pump no more blood into the pulmonary circuit than it receives from the systemic veins. The result is that in the presence of shock marked functional impairment of the left ventricle may not be accompanied by engorgement of the pulmonary circuit, because the return to the heart is so greatly diminished that it is within the capacity of even the severely damaged left ventricle. The classic example of such a state of affairs occurs in some instances of coronary thrombosis in which shock so decreases the venous return to the heart that symptoms of left ventricular failure are absent, despite a large infarct in the left ventricle.

2. When the right side of the heart fails, pulmonary engorgement is diminished, with alleviation of preexistent symptoms of failure of the left side of the heart despite the fact that the circulation time is even more protracted than previously. This is exemplified in the old observation that intensely orthopneic patients with aortic or coronary disease or hypertension may become much less dyspneic and orthopnea may regress with the appearance of such evidences of insufficiency of the right side of the heart as dependent edema and swelling of the liver.

There are also instances of isolated insufficiency of the left side of the heart in which the subjective symptoms are minimal—merely dyspnea on exertion elicited only by pointed questioning—and yet the circulation time is markedly prolonged. Indeed, in such cases the measurement of the circulation time may be the only available means of unveiling the weakness of the left ventricle. Excellent examples of this phenomenon were encountered in patients with malignant hypertension who entered the hospital with a circulation time of thirty-five seconds or more, although they complained only of headache, visual disturbances, uremic manifestations or other symptoms not correlated with heart failure.

Failure of the Left Side of the Heart with Normal Circulation Time.—In exceptional instances, the arm-to-tongue circulation time is not prolonged despite the presence of severe symptoms of failure of the left side of the heart. An example of the few cases of this type that we have encountered is the last one in table 1. This patient, with high blood pressure, had severe orthopnea, and a roentgenogram revealed intense engorgement of the lungs. Nevertheless, the arm-to-tongue circulation time was normal on two occasions and only slightly prolonged on a third measurement. The explanation would seem to be that the right ventricle is sufficiently powerful to maintain a normal velocity of the blood flow through the lungs despite the increased resistance due to the insufficiency of the left side of the heart. However, the tension in

the pulmonary circuit is increased, with resultant dyspnea and other symptoms attributable to the hypertension of the lesser circulation.

Effect of Digitalis.—We have made a number of observations which revealed that when digitalization alleviates the subjective symptoms of failure of the left side of the heart, this is evidenced objectively by diminution in the arm-to-tongue circulation time. Two such cases are listed in table 1. This observation is of interest because it furnishes additional objective evidence that digitalis may be beneficial in isolated insufficiency of the left side of the heart with normal rhythm. Although the therapeutic value of digitalis in such cases has been doubted by some clinicians, including one of us (A. M. F.), it has been especially affirmed by Harrison, Calhoun and Turley [11] on the basis of clinical observations. We have, however, observed in a number of instances of combined failure of the left and right sides of the heart that while digitalization brought the venous pressure down to normal, the reduction in circulation time was not equally pronounced, so that this still remained abnormally long.

VENOUS PRESSURE

The pressure in the peripheral veins is normal in isolated failure of the left side of the heart (table 1). Normal venous pressure is present in even very severe isolated failure of the left side of the heart. Thus, in a patient who had acute pulmonary edema due to left ventricular failure in glomerulonephritis with hypertension, the venous pressure was but 6 cm. in the presence of a circulation time of twenty-eight seconds. We have made several similar observations. It is only when the right ventricle also gives way that any considerable elevation of venous pressure develops. However, in patients with an otherwise typical clinical picture of isolated failure of the left side of the heart, the following is to be borne in mind concerning slight elevation in the venous pressure to 9 or 10 cm.: The right ventricle performs increased work because of the pulmonary hypertension due to failure of the left side of the heart. In accord with Starling's law, the right ventricle can perform this increased work only by means of greater diastolic filling and higher diastolic intraventricular tension, the latter of which is reflected in the venous pressure. It is therefore probable that slight elevation in venous pressure in the presence of failure of the left side of the heart does not per se indicate marked functional impairment of the right ventricle, but is simply a manifestation of the mechanism by which the right ventricle accommodates itself to the increased work necessitated by the

11. Harrison, T. R.; Calhoun, J. A., and Turley, F. C.: Congestive Heart Failure; Effect of Digitalis on Dyspnea and on Ventilation of Ambulatory Patients with Regular Cardiac Rhythm, Arch. Int. Med. **48**:1203 (Dec.) 1931.

pulmonary hypertension. This is perhaps also the explanation of the slight enlargement of the liver that occasionally persists unchanged for months in patients with otherwise characteristic signs of failure of the left side of the heart.

Increase in systemic venous pressure has been considered by some as an indicator of all forms of heart failure. Thus, Eyster [12] stated that "a sustained rise of general venous pressure above the upper normal limit under basal conditions invariably accompanies cardiac decompensation." The normal venous pressure in failure of the left side of the heart obviously renders this view untenable, for isolated insufficiency of the left side of the heart is a common form of cardiac decompensation and one which may last for years. Only when the right ventricle also fails does the venous pressure rise.

SUMMARY

In isolated failure of the left side of the heart the arm-to-tongue circulation time is almost always prolonged, sometimes to three times the normal value.

On the other hand, the arm-to-lung circulation time may be normal in failure of the left side of the heart despite markedly prolonged arm-to-tongue circulation time. This shows that the prolongation of the arm-to-tongue circulation time in these cases is due to slowing of the pulmonary blood flow downstream to the arterial capillaries of the lung.

The prolongation of the arm-to-tongue circulation time does not always parallel the severity of the other symptoms of failure of the left side of the heart. In exceptional cases, the arm-to-tongue circulation time is within normal limits despite severe symptoms of failure of the left side of the heart.

The circulation time in failure of the left side of the heart with normal rhythm may be shortened by digitalization, furnishing further objective evidence of the utility of digitalis in many patients with this circulatory disturbance.

The systemic venous pressure is normal in isolated failure of the left side of the heart.

12. Eyster, J. A. E.: Venous Pressure, J. A. M. A. **97**:1269 (Oct. 31) 1931.

BLOOD FAT TOLERANCE TESTS IN MALNUTRITION AND OBESITY

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I have become interested in the problem of the regulation of fat as the result of treating nondiabetic malnourished patients with insulin. When such patients are made to gain weight rapidly, fat is deposited in the subcutaneous tissues to a noteworthy degree. This is a curious fact and suggests the possibility that insulin may have an effect on the metabolism of fat as well as on the metabolism of sugar.

PLAN OF STUDY

An attempt was made to study fat tolerance in much the same manner that dextrose tolerance is customarily studied. A dose of 100 Gm. of fat in the form of 500 cc. of 20 per cent cream was employed as a test meal. This proved to be a reasonably palatable mixture, easily taken, and it never caused nausea, vomiting or diarrhea. It was administered to the patients in the morning after fasting over night. The plasma cholesterol was used as an indicator of the concentration of blood fat, because this analysis of the blood fats is the easiest to determine accurately and because, according to Joslin,[1] its percentage in plasma varies fairly consistently with the total amount of blood fat. In a number of cases the concentration of blood cholesterol was compared with that of the cholesterol ester, which has been shown by Knudson [2] to parallel the total blood lipoid following the ingestion of fat. Since the cholesterol and cholesterol esters ran hand in hand, determinations of the latter were not used as a routine procedure.

The analyses were made on 2 cc. samples of plasma, according to the method adopted by Bloor.[3] The tests [4] were made in duplicate, and all specimens obtained during a given test were read against the same standard. Samples of blood were obtained after fasting and two, four, six and eight hours after the fat meal was ingested, the patients remaining at rest during the interval and without additional food.

OBSERVATIONS ON THE BLOOD FAT TOLERANCE CURVE

In Normal Persons.—Fat tolerance tests were obtained in thirteen normal persons. The results are given in table 1.

From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Joslin, E. P.: Fat and the Diabetic, New England J. Med. **209**:519, 1933.

2. Knudson, A.: Relationship Between Cholesterol and Cholesterol Esters in the Blood During Fat Absorption, J. Biol. Chem. **32**:337, 1917.

3. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53, 1928.

4. Miss Honora F. Carroll gave technical assistance.

There was variation in the plasma cholesterol level after fasting, but comparatively little change was encountered as the result of the fat meal. The striking feature in normal people is the flatness of the cholesterol curve resulting from the ingestion of a fat meal. Rony and Levy [5] and Chaikoff, McGavack and Kaplan [6] also noted that the plasma cholesterol concentration in normal people is not affected by a fat meal.

TABLE 1.—*Fat Tolerance Tests in Normal People*

	Plasma Cholesterol Levels, Mg. per 100 Cc. of Blood Plasma				
		Hours After Test Meal*			
Case	Fasting	2	4	6	8
1	204	195	195	191	223
2	187	195	180	182	182
3	223	218	237	204	205
4	204	218	213	215	188
5	195	223	215	213	201
6	201	205	210	208	203
7	189	193	187	189	185
8	203	210	203	197	191
9	171	178	191	185	183
10	240	253	246	240	234
11	169	171	182	173	169
12	176	187	167	161	156
13	231	240	246	228	213
Average	199	207	206	199	195

* This consisted of 500 cc. of 20 per cent cream.

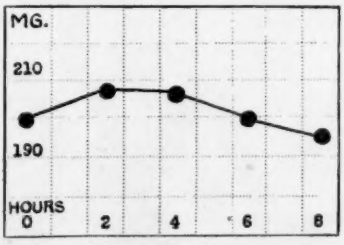

Chart 1.—Average plasma cholesterol curve obtained in thirteen normal persons after a test meal of 100 Gm. of fat. In all the charts the cholesterol is recorded in milligrams per hundred cubic centimeters of plasma and the time interval in hours.

In Malnutrition.—Fat tolerance tests were obtained in sixteen persons, who were very thin but otherwise normal, before or after and

5. Rony, H. R., and Levy, A. J.: Fat Tolerance in Obesity, J. Lab. & Clin. Med. **15**:221, 1929.

6. Chaikoff, I. L.; McGavack, T. H., and Kaplan, A.: The Blood Lipids in the Post Absorptive State and After the Ingestion of Fat in Normal Human Subjects and in a Case of Disseminated Cutaneous Xanthomata, J. Clin. Investigation **13**:1, 1934.

during a period of administration of insulin. In the cases studied during the period of treatment with insulin, 10 units of insulin was injected subcutaneously three times a day for a period before the test was made. In the cases studied after the discontinuation of insulin, at least a week was allowed to elapse before the final test was made. The results of the various tests are given in table 2.

TABLE 2.—*Fat Tolerance Tests in Malnourished People With and Without Insulin*

	Plasma Cholesterol Levels Without Insulin, Mg. per 100 Cc. of Blood Plasma					Length of Time After Omitting Insulin	Plasma Cholesterol Levels With Insulin, Mg. per 100 Cc. of Blood Plasma					Period of Insulin Therapy
		Hours After Test Meal*						Hours After Test Meal*				
Case	Fasting	2	4	6	8		Fasting	2	4	6	8	
1	157	146	139	145	128	4 months	206	237	203	197	203	2 weeks
2	152	141	139	147	156	1 week	187	198	220	160	183	6 months
3	172	176	184	167	164	3 months	199	177	166	223	166	1 week
4	199	183	193	201	203	1 week	225	234	257	231	228	7 months
5	227	206	197	193	193	2 weeks	203	219	224	202	196	2 months
6	267	272	259	250	237	2 years	215	247	254	228	206	9 days
7	197	234	243	223	220	5 months	220	238	250	200	208	10 days
8	187	192	163	158	156	8 months	208	229	240	211	205	1 week
9	218	223	210	195	191	8 days	164	183	187	171	153	2 weeks
10	190	200	178	180	176	Before insulin	208	237	264	223	206	2 weeks
11	220	225	231	228	213	Before insulin	191	208	215	259	201	1 week
12	184	203	178	182	188	Before insulin	178	186	192	204	182	3 weeks
13	172	142	168	170	153	Before insulin	178	195	180	165	161	8 days
14	234	237	223	218	215	Before insulin	191	195	205	201	189	2 weeks
							228	237	246	240	225	2 months
15	215	225	220	199	197	Before insulin	216	241	251	226	210	3 weeks
16	199	195	198	187	178	Before insulin						
Aver.	199	200	195	190	185		201	217	222	212	195	

* This consisted of 500 cc. of 20 per cent cream.

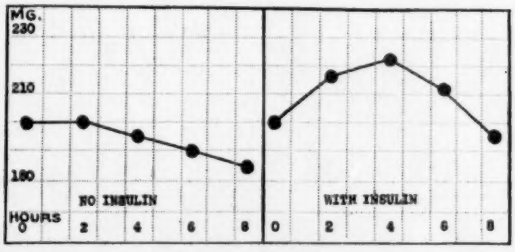

Chart 2.—Average plasma cholesterol curves obtained in sixteen thin people following the fat meal, before or after and during a period of treatment with insulin.

As in the strictly normal group, there was more or less variation in the plasma cholesterol level after fasting during the various periods of observation, but the average curve noted following the fat meal without insulin was much as in the normal person. In certain cases there appeared to be a less than normal rise in the curve and a sharper than

normal fall, suggesting either deficient absorption of the fat meal or its more rapid passage through the blood.

The curves for plasma cholesterol obtained during the period of administration of insulin were strikingly different. Here the plasma cholesterol concentration rose sharply and remained elevated for several hours after the ingestion of the cream, decreasing to near the fasting level at the end of the period of observation. These results do not confirm the experimental work on dogs by Rony and Ching,[7] who found that insulin inhibits alimentary lipemia, of White,[8] who showed that insulin has no constant effect on the blood cholesterol level, or of Christomanos,[9] who believed that insulin lowers the serum fat level of normal subjects.

In Obesity.—It was of interest to compare the cholesterol curves obtained in thin people fattening under insulin therapy with the curves

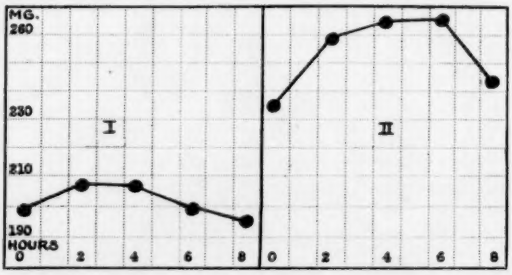

Chart 3.—Comparison of average plasma cholesterol curves obtained in thirteen normal (*I*) and twenty-one obese (*II*) people after the test meal of 100 Gm. of fat.

normally obtained in untreated obese persons. For this purpose a group of twenty-one patients who were considerably overweight for their height, age and sex were selected. The weights of these subjects ranged from 131 to 275 pounds (59.4 to 124.7 Kg.), and each was at least 20 pounds (9.1 Kg.) over standard weight for age, sex and height, many being from 50 to 117 pounds (22.7 to 53.1 Kg.) overweight. The results of the tests are given in table 3.

There was considerable variation encountered in the plasma cholesterol level after fasting, many of the group having after fasting hypercholesteremia of varying degree. After the test meal there was likely to be a marked rise in the cholesterol curve which persisted for several hours, tending to return to near the level of fasting toward

7. Rony, H. R., and Ching, T. T.: Effect of Insulin on Alimentary Lipemia in Normal Dogs, Proc. Soc. Exper. Biol. & Med. **27**:533, 1930.

8. White, A. C.: Insulin and the Blood Fat, Biochem. J. **19**:921, 1925.

9. Christomanos, A. A.: Ueber den Einfluss des Insulins auf die Fettverteilung im Serum, Biochem. Ztschr. **214**:482, 1929.

the end of the period of observation. The curves were strikingly similar to those obtained in thin people during a period of insulin therapy.

Effect of Extract of Pituitary in Obesity.—In a series of experiments carried out on dogs, Raab [10] demonstrated that extract of pituitary causes the blood fat level to fall. His observation may be accounted for in part by the marked increase in fatty acids in the liver which Coope and Chamberlain [11] showed are laid down in animals following the administration of extract of pituitary. Raab's experiments are

TABLE 3.—*Fat Tolerance Tests in Obese Patients*

Case	Plasma Cholesterol Levels, Mg. per 100 Cc. of Blood Plasma					Weight, Pounds	Overweight, Pounds
	Fasting	Hours After Test Meal*					
		2	4	6	8		
1	189	229	312	246	217	170	25
2	203	218	220	254	208	226	48
3	250	275	288	272	237	250	92
4	456	492	506	526	506	204	71
5	234	257	293	237	231	211	73
6	234	279	297	275	263	200	47
7	201	231	240	312	263	131	26
8	228	254	261	260	206	161	36
9	218	228	263	243	225	180	28
10	249	312	318	328	263	170	20
11	213	228	237	225	210	235	115
12	220	237	246	237	225	220	90
13	183	183	171	178	176	224	74
14	328	367	...	360	307	142	22
15	220	237	240	231	243	162	36
16	220	228	228	215	215	236	66
17	225	234	240	260	243	212	60
18	215	228	231	225	228	275	117
19	197	203	215	220	208	243	115
20	234	253	263	246	246	215	75
21	218	243	218	225	208	200	50
Average	235	258	264	265	244		

* This consisted of 500 cc. of 20 per cent cream.

convincing and suggest that the pituitary gland plays an important part in the regulation of fat metabolism. Since marked changes in the cholesterol level after a fat test meal were obtained in obese people, it seemed of interest to determine whether extract of pituitary could demonstrably change the reactions and produce results like those described by Raab.

Fat tolerance tests were made in nine obese patients on one day without the administration of extract of pituitary and then several days later after they had received extract of pituitary. The preparation was admin-

10. Raab, W.: The Rôle of the Pituitary Posterior Hormone in Fat Metabolism, Endocrinology **14**:385, 1930.

11. Coope, R., and Chamberlain, E. N.: The Effect of Pituitrin on the Fatty Acid of the Liver, J. Physiol. **60**:69, 1925.

istered intranasally, according to Blumgart's method [12] for treating diabetes insipidus. A small piece of cotton was soaked in extract of the posterior lobe of the pituitary of obstetric strength so that about 1 cc. of the solution was absorbed. Immediately after the ingestion of the cream the cotton pledget was placed in a nostril just above the middle turbinate and was left in place, being refreshed every two hours, just after the specimens of blood were taken. Such a procedure allowed continuous absorption of the extract of pituitary over a long period of time. In a few cases

TABLE 4.—*Fat Tolerance in Obese Patients Taking Extract of Pituitary*

	Plasma Cholesterol Levels, Mg. per 100 Cc. of Blood Plasma									
	No Pituitary Administered					Pituitary Administered*				
		Hours After Test Meal†					Hours After Test Meal†			
Case	Fasting	2	4	6	8	Fasting	2	4	6	8
1.....	201	231	240	312	263	206	205	203	214	199
2.....	249	312	318	328	263	223	234	228	228	225
3.....	213	228	237	225	210	205	208	197	203	203
4.....	220	237	240	231	243	223	220	208	201	195
5.....	220	228	228	215	215	213	203	201	210	208
6.....	456	492	506	526	206	323	353	360	328	347
7.....	215	228	231	225	228	228	215	228	218	218
8.....	234	279	297	275	263	210	225	234	231	228
9.....	197	203	215	220	208	208	197	193	195	195
Average....	245	271	279	284	233	227	229	228	225	224

* Extract of pituitary was administered intranasally immediately after each specimen of blood was taken.

† This consisted of 500 cc. of 20 per cent cream.

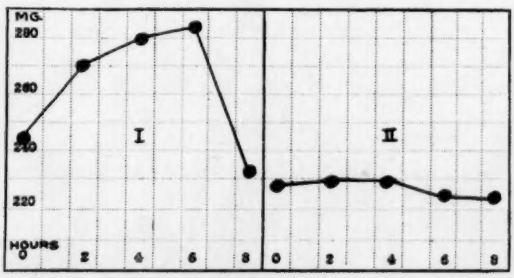

Chart 4.—Average plasma cholesterol curves obtained in nine obese persons following the test meal of 100 Gm. of fat, with (*II*) and without (*I*) administration of extract of pituitary.

0.5 or 1 cc. of the extract was administered intramuscularly every two hours, but as the results obtained by the intranasal method of administration were practically identical with those obtained when the drug was administered hypodermically, the latter method was discontinued because of the discomfort involved. The results of the tests are given in table 4.

12. Blumgart, H. L.: Diabetes Insipidus with Particular Reference to Further Experience with Treatment by Pituitary Posterior Lobe Extract Applied Intranasally, M. Clin. North America **15**:895, 1932.

There was a typical rise in the plasma cholesterol level in the obese patients as the result of the fat meal, but when extract of pituitary also was administered, comparatively little variation in the plasma cholesterol concentration was encountered. Extract of pituitary appeared to prevent a significant rise in the cholesterol level and in a few instances seemed actually to cause a decrease in the cholesterol level below the concentration after fasting, so that the resultant curves were similar to those found in certain of the normal thin subjects.

TABLE 5.—*Fat Tolerance in Patients with Diabetes Insipidus Taking Extract of Pituitary*

	Plasma Cholesterol Levels, Mg. per 100 Cc. of Blood Plasma									
	No Pituitary Administered					Pituitary Administered*				
		Hours After Test Meal†					Hours After Test Meal†			
Case	Fasting	2	4	6	8	Fasting	2	4	6	8
1.....	256	289	308	318	338	238	250	264	264	240
2.....	240	249	263	271	297	240	243	243	253	240
3.....	187	195	223	234	231	180	189	185	168	171
4.....	187	195	205	215	199	187	183	180	185	191
5.....	201	215	225	228	237	208	201	205	197	187
6.....	201	213	234	228	225	195	201	205	191	191
7.....	234	257	220	225	228	234	208	205	201	166
Average....	215	230	240	246	254	212	211	212	208	198

* Extract of pituitary was administered intranasally immediately after each specimen of blood was taken.
† This consisted of 500 cc. of 20 per cent cream.

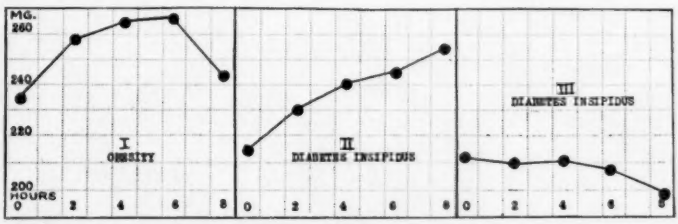

Chart 5.—Comparison of average plasma cholesterol curves obtained following the test meal of 100 Gm. of fat in seven patients with diabetes insipidus, with (*III*) and without (*II*) administration of extract of pituitary and in twenty-one obese persons who did not receive treatment (*I*).

Extract of Pituitary in Diabetes Insipidus.—These observations were so striking that finally it appeared logical to test the fat tolerance of certain persons known to have insufficiency of the pituitary gland. For this purpose seven patients with diabetes insipidus were studied. Although it may be argued that the tuber cinereum or other structures allied to the pituitary gland are at fault in this disease, nevertheless the administration of extract of pituitary admittedly relieves the symp-

toms of polyuria and excessive thirst in most cases. The results of the fat tolerance tests in this group are given in table 5.

Without extract of pituitary there was a marked rise of the plasma cholesterol concentration following the ingestion of cream, similar to that observed in the obese subjects. In cases 1, 2 and 5 the cholesterol level continued to rise during the entire eight hour period of observation. In no case did the cholesterol curve appear to depend on the patient's state of nutrition because certain of the patients were thin and none were remarkably fat. When extract of pituitary was administered after the ingestion of cream and at two hour intervals subsequently, the plasma cholesterol level was flattened, showing a normal type of reaction.

COMMENT

The proper explanation of the results obtained in this study is, at present, uncertain. Certainly these data suggest that both insulin and extract of pituitary modify appreciably the type of blood fat curves obtained after a fat meal, insulin causing a rise in blood fat concentration and extract of pituitary a fall. That insulin and extract of pituitary have antagonistic effects on the blood sugar level has already been pointed out by Burn [13] and Blotner and Fitz.[14] The data recorded here suggest that the two substances likewise influence the blood fat level and in opposite ways.

The appearance of an increase in the plasma cholesterol level following the administration of insulin and cream in thin people suggests that insulin may cause an increase in the rate of absorption of fat from the gastro-intestinal tract or possibly that, owing to the presence of insulin, the cholesterol is not removed from the blood as rapidly as usual. That insulin increases the absorption of food and dextrose has already been proposed by Koref and Mautner [15] and Blotner.[16]

The striking similarity between the fat tolerance curves obtained in obese persons and in thin people receiving insulin suggests the possibility that there may be available an increased amount of insulin in obesity, this accounting for the rise in the plasma cholesterol level which was noted following the ingestion of cream. If this assumption is cor-

13. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and Other Substances, J. Physiol. **57**:318, 1923.

14. Blotner, H., and Fitz, R.: The Effect of Insulin, Pituitrin and Adrenalin on the Blood Sugar Level, J. Clin. Investigation **5**:51, 1927.

15. Koref, O., and Mautner, H.: Zur Resorptionsbeschleunigung durch Insulin, Klin. Wchnschr. **5**:191, 1926.

16. Blotner, H.: Observations on the Effect of Insulin in Thin Persons, J. A. M. A. **100**:88 (Jan. 14) 1933; Insulin and Sugar Tolerance in Thin People, Arch. Int. Med. **53**:153 (Jan.) 1934.

rect, it would explain satisfactorily the increased appetite so often met with in obese people.

On the other hand, the results after the administration of extract of pituitary are equally striking. Extract of pituitary appears to decrease the plasma cholesterol concentration after a test meal of fat. This decrease in blood fat has been shown at least in part to be due to the deposit of fat in the liver by extract of pituitary. There is also the possibility that extract of pituitary acts on the intestines, inhibiting the absorption of fat. Finally, pituitary dysfunction may be the cause of obesity in certain persons, as has been suggested by Dercum,[17] Cushing [18] and others. Perhaps obesity in general is associated with varying degrees of pituitary insufficiency. Such an idea is supported to some extent by the similarity of cholesterol curves obtained after the ingestion of cream by patients with diabetes insipidus and by obese patients, both being influenced by the administration of extract of pituitary.

TREATMENT OF OBESITY WITH EXTRACT OF PITUITARY

Assuming from the results of the tests that in obesity there may be hypofunction of the pituitary gland, it appeared logical to apply this idea clinically in treatment. Consequently, an effort was made to determine whether obese persons could be made to lose weight with the administration of extract of pituitary and without any other form of treatment.

Extract of pituitary was administered intranasally three times a day after meals to a group of six obese people, the cotton pledget being retained in the nose for two hours after each application. No dietetic restrictions were advised; in fact, the patients were encouraged to eat normally and to take as much food as they desired. Although the series is small and the patients have been observed for but a short period of time, yet the immediate results appear to be of some interest. So far, in each case there has been an average loss of weight of from 1½ to 2 pounds (0.75 to 0.9 Kg.) a week under this management. The greatest amount of weight lost thus far by any one patient is 17 pounds (7.7 Kg.) in ten weeks. Obviously it will require a much longer period of time to test the efficacy of such a method of treatment of obesity.

SUMMARY AND CONCLUSIONS

This paper presents a study of alimentary fat tolerance, using the plasma cholesterol as an indicator of the blood fat concentration, and as a test meal 500 cc. of 20 per cent cream.

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17. Dercum, F. X., and McCarthy, D. J.: Autopsy in a Case of Adiposa Dolorosa, Am. J. M. Sc. **124**:994, 1902.

18. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

In normal persons the plasma cholesterol level following the ingestion of such a test meal remains practically unchanged during an eight hour period.

In thin persons the cholesterol level after such a test meal remains unchanged or even shows a decrease. Under insulin therapy, however, there is a significant rise in the cholesterol level after such a test meal.

In obese persons there is a marked rise in the cholesterol level after such a test meal. The blood fat curve in obesity is similar to that obtained in malnourished people receiving insulin.

In diabetes insipidus after such a test meal the cholesterol level increases markedly, and the resultant curve is similar to that obtained in obesity.

Extract of pituitary administered intranasally modifies the plasma cholesterol curve obtained after a fat test meal in patients with obesity and diabetes insipidus. Extract of pituitary prevents the development of hyperlipemia which otherwise occurs.

Insulin and extract of pituitary have effects on fat as well as on sugar metabolism that are of opposite nature, insulin causing a rise in the blood fat concentration after a fat meal and extract of pituitary a fall.

In a group of six obese patients treated for short intervals with applications of extract of pituitary intranasally and without diet there has been an average weekly loss of from 1½ to 2 pounds. The greatest amount of weight lost under this form of therapy by any one patient has been 17 pounds in ten weeks. Although these results are of some interest, no definite conclusions can be drawn regarding their significance. The possibilities of such a method of treating obesity will remain uncertain until further studies have been completed.

23 Bay State Road.

SIGNIFICANCE OF THE PHENOLSULPHONPHTHALEIN TEST OF RENAL FUNCTION

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LA JOLLA, CALIF.
AND
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SAN FRANCISCO

The aim of any test of biologic function is to determine the existing function of an organ or tissue in relation to the function if the tissue or organ and organism as a whole were normal. A quantitative consideration is necessary for the proper evaluation of any function. In the case of the kidney, an attempt to measure the amount of functioning renal tissue must be the aim of any test of function. The test with phenolsulphonphthalein (phenol red) is probably the most widely used, at least in this country, of the numerous tests of renal function which have been proposed, and it is the purpose of the present study to inquire to what degree it meets the criteria. When the test was first described by Rowntree and Geraghty,[1] it was found experimentally that the removal of half the normal renal tissue was without influence on the results of the test. However, the idea has grown up that the normal excretion of the dye indicates unimpaired renal function, a conclusion which is obviously incorrect. We are unaware of any study in which a constant relation of the test to the functioning renal tissue has been demonstrated. The mode of excretion of the dye by the kidney is uncertain,[2] but there is evidence [3] that it is excreted in a manner similar to that of urea. On theoretical grounds it would therefore be surprising if consistent results were obtained with the phenol red test, as ordinarily performed, for the speed of excretion of an administered quantity of

From the Scripps Metabolic Clinic, La Jolla, Calif., and the Department of Medicine, Stanford University School of Medicine, San Francisco.

1. Rowntree, L. G., and Geraghty, J. T.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonphthalein, J. Pharmacol. & Exper. Therap. **1**:579, 1910.

2. Richards, A. N.: Methods and Results of Direct Investigations on the Functions of the Kidney, Baltimore, Williams & Wilkins Company, 1929. Marshall, E. K., Jr.: The Secretion of Phenol Red by the Mammalian Kidney, Am. J. Physiol. **99**:77, 1931.

3. MacKay, E. M., and Oliver, J.: A Comparison of the Method of Excretion of Neutral Red and Phenol Red by the Mammalian Kidney, J. Exper. Med. **51**: 161, 1930.

urea could give only the vaguest idea of the renal function. In several respects, however, the excretion of the dye is different. The dye is given intravenously, while urea is administered by mouth; hence the urea reaches the blood stream and becomes available to the kidney in an uncertain length of time. In determining the percentage of excretion of phenol red the base-line is zero, while with urea the base-line is a variable and uncertain level which is determined by a large number of factors. It is probably these differences which give the phenolsulphonphthalein test the value which it appears to have under certain conditions.

An attempt was first made to determine the relation between the percentage excretion of the dye and the size of the kidney in normal rabbits. Here, of course, it was necessary to vary the size of the kidney and of the entire organism together, a factor which may have been responsible for our failure to find any relationship. When 6 mg. of dye was injected intravenously, small rabbits with relatively small kidneys were found to excrete practically as much during the ensuing two hours as large rabbits with larger renal organs. Likewise, there was no relation between the percentage of dye excreted and the weight of the kidneys when the dose of dye was made approximately the same as that for man (3 mg. per square meter) on the basis of body surface or was increased to make allowance for the fact that the rabbit has about five times as much kidney as man in relation to body mass, when this is measured as body surface.

Observations on normal persons were equally unsatisfactory so far as a constant relation to the probable weight of the kidney was concerned. We have gained the impression that a relation between the percentage excretion of phenol red and renal weight may be demonstrated only when the body mass remains essentially constant, while the amount of functioning renal tissue is varied. This condition existed in a group of patients suffering from Bright's disease, in whom there were varying degrees of impairment of renal function. In this group the phenolsulphonphthalein test was compared with the amount of functioning renal tissue as measured by Addis' procedure.[4]

TEST OF RENAL FUNCTION

The Phenolsulphonphthalein Test.—The dye test was carried out in the usual manner. There was no alteration in the patients' daily routine, and the test was generally performed in the morning. Fifteen minutes before the dye was given

4. Addis, T.: Renal Function and the Amount of Functioning Tissue, Arch. Int. Med. **30**:378 (Sept.) 1922.

the patient received 400 cc. of water. Fifteen minutes later the subject voided completely, and within two or three minutes 1 cc. of the commercial dye solution containing 6 mg. of the monosodium salt of phenolsulphonphthalein was injected intravenously from a tuberculin syringe. It is generally agreed that any other method of administration than the intravenous route gives inconsistent results, for the amount of dye which is actually available to the kidney is then an unknown quantity. Exactly one and two hours after the injection of the dye, complete samples of urine were collected, and the amount of dye excreted was determined by comparison in a Duboscq colorimeter with a standard solution prepared from the same lot of dye as that used for injection. If the excretion of dye proved to be higher in the second hour than in the first, the test was discarded, for this was considered evidence of an obstruction of the urinary tract or of retention in the bladder and consequently a false indication of the renal excretion of the dye.

The Addis Test.—This test measures the amount of functioning renal tissue and depends on the determination under certain standard conditions of the ratio $\frac{\text{urine urea rate}}{\text{blood urea concentration}}$. The evidence that the procedure actually measures the amount of functioning renal tissue may be summarized briefly as follows: Considered as the volume of blood which is freed by the kidneys of urea per unit of time,[5] it is a reasonable measure of renal function. Under the standard conditions the ratio is remarkably constant for a given subject.[6] In normal rats,[7] rabbits [8] and dogs [9] the ratio bears a direct linear relationship to the actual weight of the kidneys. In rabbits with nephritis induced by uranium the renal function, as measured in this manner, has been shown [10] to vary with the amount of functioning renal tissue, as approximated anatomically. When half the renal tissue is removed by unilateral nephrectomy the ratio is cut in half,[11] and as compensatory hypertrophy of the remaining kidney ensues the ratio follows closely the development

5. (*a*) Addis, T., and Watanabe, C. K.: A Method for the Measurement of the Urea Excreting Function of the Kidneys, J. Biol. Chem. **28**:251, 1916. (*b*) Addis, T.: The Renal Lesion in Bright's Disease, Am. J. M. Sc. **176**:623, 1928. (*c*) Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, P. B. Hoeber, Inc., 1931.

6. Addis, T., and Drury, D. R.: The Rate of Urea Excretion: V. The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, J. Biol. Chem. **55**:105, 1923. Polland, W. S.: The Effect of Some Diuretics on the Urea-Excreting Capacity of the Kidney, Am. J. Physiol. **85**:141, 1928.

7. MacKay, E. M., and Raulston, B. O.: Factors Which Determine Renal Weight: XI. Renal Function, J. Exper. Med. **53**:109, 1931.

8. Taylor, F. B.; Drury, D. R., and Addis, T.: The Relation Between the Rate of Urea Excretion and the Size of the Kidney, Am. J. Physiol. **65**:55, 1923.

9. MacKay, E. M.: A Comparison of the Relation Between the Rate of Urea Excretion and the Amount of Renal Tissue in the Dog and Other Mammals, Am. J. Physiol. **100**:402, 1932.

10. Watanabe, C. D.; Oliver, J., and Addis, T.: Determination of the Quantity of Secreting Tissue in the Living Kidney, J. Exper. Med. **28**:359, 1918.

11. Addis, T.; Myers, B. A., and Oliver, J.: The Effect of Unilateral Nephrectomy on the Function and Structure of the Remaining Kidney, Arch. Int. Med. **34**:243 (Aug.) 1924.

of the hypertrophy as measured anatomically.[12] In man the ratio is also proportional to the body surface, while the body surface and the weight of the kidneys are, in turn, in straight-line association.[13]

The details of the Addis ratio test have already been described.[5c] The normal value for the ratio, $\frac{\text{urea in a one hour specimen of urine}}{\text{urea in 100 cc. of blood}}$, under the standard conditions is 27.7 per square meter of body surface.[14] Our results are expressed as percentages of this normal value.

Data.—Our figures are based on one hundred and thirty-nine observations on eighty-two patients with Bright's disease. The phenolsulphonphthalein and the Addis ratio test were made not longer than three days apart. On the day before the measurement of the ratio the blood urea concentration was determined for comparison of its relation to the functioning renal tissue[15] with that of the phenolsulphonphthalein test.

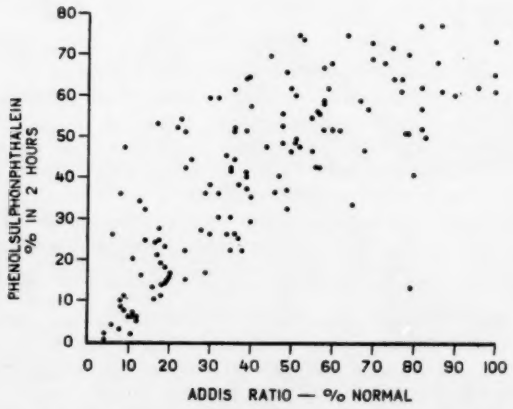

Chart 1.—A scatter diagram showing the relation of the excretion of phenolsulphonphthalein to the Addis ratio.

The results of the individual observations on the excretion of phenolsulphonphthalein are shown in the scatter diagram (chart 1). The picture is similar to that of the relation of the phenolsulphonphthalein test to the standard blood urea

12. Oliver, J.: The Regulation of Renal Activity: X. The Morphologic Study of the Effect of Unilateral Nephrectomy on the Function and Structure of the Remaining Kidney, Arch. Int. Med. **34**:258 (Oct.) 1924.

13. MacKay, E. M.: Kidney Weight, Body Size and Renal Function, Arch. Int. Med. **50**:590 (Oct.) 1932.

14. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p. 155. Addis and Oliver.[5c] McKay.[13]

15. MacKay, E. M., and MacKay, L. L.: The Relation Between the Blood Urea Concentration and the Amount of Functioning Renal Tissue, J. Clin. Investigation **4**:127, 1927.

clearance test of Van Slyke.[16] As with the blood urea concentration,[15] the normal values for phenolsulphonphthalein may be obtained until the renal function is reduced to less than half of normal.

Statistical Analysis.—One of us (D. A. R.) has pointed out elsewhere [17] that it is possible by statistical analysis to determine the clinical value of tests of function, not only through their correlation, but also through the shape of their regression, with the amount of functioning tissue which it is designed to measure. These factors seem equally important. In the present instance it is known that the Addis ratio represents the functioning renal tissue. The tests of excretion of

TABLE 1.—*Statistical Characteristics of the Addis Ratio (per Cent of Normal) with Blood Urea Concentration and Excretion of Phenolsulphonphthalein*

Characteristics of Addis Ratio*	Phenolsulphonphthalein, per Cent Excreted in Two Hours	Blood Urea, Mg. per 100 Cc.
r	+0.757 ± 0.024	−0.630 ± 0.034
$\frac{\eta xy}{\zeta/P.E.\zeta}$	+0.749	−0.682 −2.38
$\frac{\eta yx}{\zeta/P.E.\zeta}$	+0.791 2.04	−0.805 5.02
M_x	42.60 ± 1.45	42.60 ± 1.45
M_y	40.90 ± 1.16	57.62 ± 2.47
σx	25.29 ± 1.02	25.29 ± 1.02
σy	20.34 ± 0.82	43.15 ± 1.75
N	139	139

* The Addis ratio is denoted by x in each instance, the other variables by y. The regression of the Addis ratio on the phenolsulphonphthalein excretion was $x = 0.941y + 4.1$, and the regression of phenolsulphonphthalein on the Addis ratio was $y = 41.16 + 0.2315x - 42.93e^{-0.0478x}$. The relation of the Addis ratio and the blood urea concentration was $xy = 1{,}755$.

phenolsulphonphthalein and blood urea concentration are to be evaluated. The statistical terms are described and a more complete description of the methods used is given elsewhere.[18] In table 1 are presented the statistical characteristics of the observations under consideration. Tables 2 and 3 are the correlation tables, with the regression data in the margins.

16. Van Slyke, D.; McIntosh, F. T.; Möller, E.; Hannon, R. R., and Johnston, C.: Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, J. Clin. Investigation **8**:363, 1930.

17. Rytand, D. A.: The Rate of Excretion of Urine in Subjects with Different Amounts of Renal Tissue, J. Clin. Investigation **11**:1153, 1933.

18. Pearl, R.: Introduction to Medical Biometry and Statistics, ed. 2, Philadelphia, W. B. Saunders Company, 1930. Rytand.[17]

TABLE 2.—*The Correlation of the Addis Ratio and the Excretion of Phenolsulphonphthalein*

Phenolsulphonphthalein, per Cent Excreted in Two Hours	Addis Ratio, per Cent of Normal																					Means of Ratio
	0-4.9	5-9.9	10-14.9	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	75-79.9	80-84.9	85-89.9	90-94.9	95-99.9	Total	
75 to 79	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1	..	..	2	73.10
70 to 74	..	..	..	..	..	..	..	..	..	..	2	..	1	..	1	1	..	..	..	1	6	
65 to 69	..	..	..	..	..	..	..	..	..	2	..	1	1	..	2	1	..	1	..	..	8	68.25
60 to 64	..	..	..	..	..	..	..	3	..	..	1	1	..	..	..	2	1	1	..	3	12	
55 to 59	..	..	..	..	..	..	2	..	1	..	1	2	..	2	..	1	1	..	1	..	11	52.50
50 to 54	..	..	..	1	3	..	..	3	..	2	..	4	2	..	..	1	1	..	..	..	17	
45 to 49	..	1	..	..	..	..	1	..	1	1	4	1	..	1	..	1	1	..	..	..	12	48.15
40 to 44	..	..	..	..	1	1	..	5	..	1	..	2	..	..	..	..	1	..	..	..	11	
35 to 39	..	1	..	..	..	1	2	2	1	2	..	..	..	..	..	..	..	..	..	..	9	34.80
30 to 34	..	..	2	..	..	..	1	1	..	1	..	..	..	1	..	..	..	..	..	..	6	
25 to 29	..	1	..	1	..	1	2	1	1	..	..	..	..	..	..	..	..	..	..	..	7	25.15
20 to 24	..	..	2	4	1	..	..	3	..	..	..	..	..	..	..	..	..	..	..	..	10	
15 to 19	..	..	1	2	3	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	7	21.25
10 to 14	..	2	..	6	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	9	
5 to 9	..	3	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	6	8.75
0 to 4	2	2	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	6	
Total	2	10	10	14	8	4	8	18	4	9	8	11	4	4	3	8	6	3	1	4	139	
Means of phenolsulphonphthalein	14.15		18.10		33.30		41.75		46.70		54.85		55.00		58.40		60.85		63.50			

TABLE 3.—*The Correlation of the Addis Ratio and the Blood Urea Concentration*

Blood Urea, Mg. per 100 Cc.	Addis Ratio, per Cent of Normal																				Total	Means of Ratio
	0-4.9	5-9.9	10-14.9	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	75-79.9	80-84.9	85-89.9	90-94.9	95-99.9		
260 to 279	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	2.50
240 to 259	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	....
220 to 239	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	....
200 to 219	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	5.00
180 to 199	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	7.50
160 to 179	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	7.50
140 to 150	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2	10.00
120 to 139	..	1	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	12.50
100 to 119	..	3	1	2	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	7	13.20
80 to 99	..	..	5	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	6	14.15
60 to 79	..	1	1	4	1	..	2	6	2	..	1	..	1	..	..	..	..	..	..	..	19	31.70
40 to 59	..	..	1	3	5	3	3	3	1	3	3	1	2	1	1	1	1	2	..	..	34	43.25
20 to 39	..	..	..	4	..	1	3	9	1	6	4	10	1	3	2	4	3	1	1	3	56	55.05
0 to 19	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3	2	..	..	1	6	82.50
Total.....	2	10	10	14	8	4	8	18	4	9	8	11	4	4	3	8	6	3	1	4	139	
Means of blood urea.....	160.0		77.4		58.2		46.8		42.2		36.4		42.4		28.2		32.2		26.0			

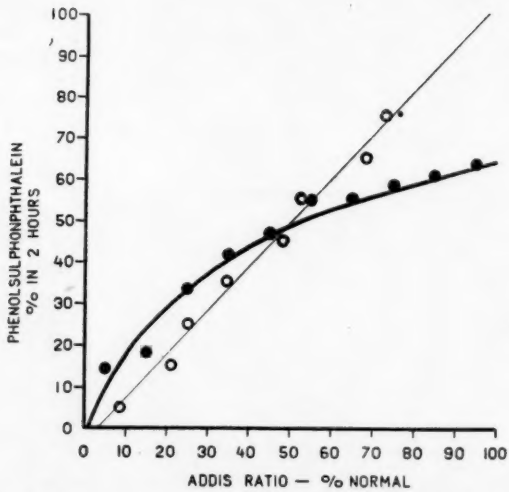

Chart 2.—The heavy line shows the regression of the Addis ratio (per cent of normal) on phenolsulphonphthalein: $x = 0.941y + 4.10$. The light line shows the regression of the phenolsulphonphthalein excretion on the Addis ratio: $y = 41.16 + 0.2315x - 42.93e^{-0.0478x}$. In each case the Addis ratio is denoted by x, the other variable by y.

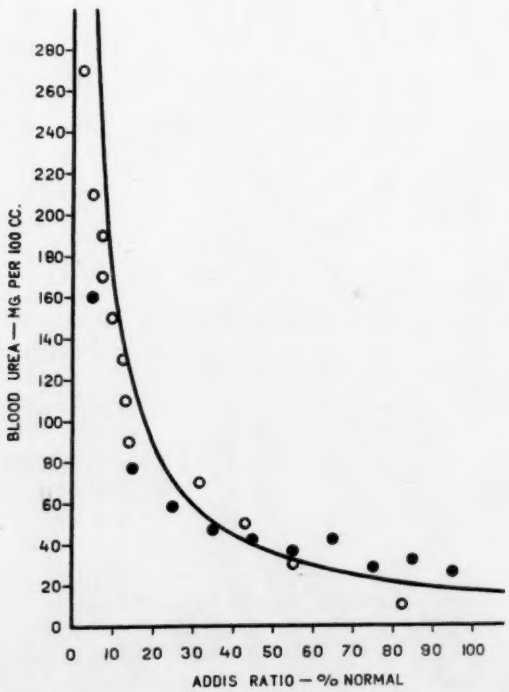

Chart 3.—The solid dots represent the regression of blood urea on the ratio and the open dots, the regression of the ratio on the blood urea. The relationship of the Addis ratio (per cent of normal) and blood urea is $xy = 1{,}755$. The Addis ratio is denoted by x; the blood urea by y.

COMMENT

In figure 2, the heavy line with solid dots represents the regression of the phenolsulphonphthalein excretion on the ratio. Physiologically and for comparison with other tests it is the most interesting. Practically, the light straight line, which represents the regression of the ratio on the phenolsulphonphthalein excretion and predicts the ratio from the phenolsulphonphthalein excretion is of more concern here. The equation is almost $x = y$, and for clinical purposes is close enough. It is convenient to know that, for example, if 40 per cent of the injected dye is excreted in two hours, the most likely ratio is 40 per cent.

In figure 3 have been plotted the regression of blood urea on the ratio (solid dots) and of the ratio on blood urea (light dots). They indicate similar regression lines. For reasons which will be considered in more detail elsewhere and which are inherent in the ratio formula, $\frac{UV}{B}$ = ratio, the blood urea-ratio curve should be a rectangular hyperbola, equation $xy = k$, or the blood urea times the ratio equals a constant, the rate of excretion of urea. This constant is 1,755 in the present data, which fit the theoretical curve fairly well. Clinically, then, one divides 1,755 by the blood urea to get the per cent of the normal ratio.

Rytand [17] calculated the odds of prediction of the amount of functioning renal tissue from other variables. The same thing has been done here: The ratio is predicted from the blood urea excretion by dividing 1,755 by the observed urea concentration, and from the phenolsulphonphthalein excretion by the formula, percentage of phenolsulphonphthalein excretion equals ratio (instead of the more accurate mathematical regression of $0.941y + 4.1$). The predictions in the one hundred and thirty-nine tests were compared with the actual ratios and the root-mean-square deviations of the errors calculated. The deviations were 16.71 for phenolsulphonphthalein and 19.10 for urea concentration. These results mean roughly that the odds are 2.15 to 1 in favor of a prediction being within $\pm$ 17 per cent of the true value when phenolsulphonphthalein is used, and within — 19 per cent when the blood urea concentration is used to estimate the amount of functioning renal tissue (always in per cent of normal). The correlations are obviously better when the renal function is low. Separating the observations, the deviations are such that the odds are 2 to 1 in favor of the ratio predicted from the phenolsulphonphthalein excretion being $\pm$ 19.5 per cent of the true value when the observed excretion of phenolsulphonphthalein is 45 per cent of the injected amount or higher and $\pm$ 13.5 per cent when it is lower. Predicting from the blood urea concentration, the odds are 2 to 1 that the ratio will be $\pm$ 15.4 per cent of the true value when the observed blood urea concentration is 40 mg. per hundred cubic centimeters or higher and $\pm$ 22.9 per cent when the observed blood urea concentration is lower than 40.

Of the two variables examined here the phenolsulphonphthalein test is by far the best measure of functioning renal tissue, not so much because it has a comparatively high correlation with the Addis ratio but because it happens to have a linear regression. On the basis of correlation with the ratio and the shape of the regression, a comparison of these variables with others which have been studied in the same manner [17] reveals that in order of value as measures of functioning renal tissue may be listed the "maximum rate of urine excretion," the excretion of phenolsulphonphthalein, the blood urea concentration and the specific gravity concentration. However, for practical purposes, because it is much easier for the physician and the patient and is most apt to be measured accurately, the phenolsulphonphthalein test may be considered the most valuable method of measuring function in the group.

The physiologic significance of the blood urea concentration-ratio regression in figure 3 will be considered elsewhere. The regression line of the excretion of phenolsulphonphthalein on the ratio in figure 2 falls smoothly along a parabola which may be extended to meet the origin. The excretion of phenolsulphonphthalein begins to decrease slightly when the amount of renal tissue becomes less than normal. When 50 per cent of the kidney has been removed the decrease in the excretion of phenol red becomes more and more rapid as the amount of renal tissue is reduced further.

SUMMARY

The significance of the phenolsulphonphthalein test of renal function and, secondarily, of the blood urea concentration was determined by a statistical analysis of the variables in relation to the Addis ratio as a measure of the amount of functioning renal tissue in a group of patients with Bright's disease.

Judged by their correlation and by the shape of their regression line with the ratio the phenolsulphonphthalein test is superior to the blood urea concentration as a measure of the amount of functioning renal tissue.

For certain clinical purposes the Addis ratio may be predicted as a per cent of normal from the blood urea by dividing 1,755 by the blood urea concentration and from the phenolsulphonphthalein test by multiplying the percentage of the dye excreted by 1.

The odds are 2 to 1 that the ratio may be predicted within a range of ± 17 per cent by means of the phenolsulphonphthalein test and of ± 19 per cent by means of the blood urea concentration.

Considering the individual observations, it is shown that both the blood urea concentration and the excretion of phenolsulphonphthalein may be well within normal limits until at least half the normally functioning renal tissue has been destroyed.

Progress in Internal Medicine

ALLERGY

A REVIEW OF CURRENT LITERATURE

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From January to June 1934, the *Quarterly Cumulative Index* lists under the heading "Anaphylaxis and Allergy" 206 titles. In 1933 there were 166 titles whereas five years before, in 1928, there were only 126 titles. Interest in the subject is growing rapidly in accordance with the discovery that the peculiar reaction of the host which is called "allergy" applies not only to hay fever, asthma and eczema but to a good many of the infectious diseases. The study of the host and the responses of the host to injuries and insults of wide variety is attracting the attention which it deserves. The subject is important. Even at this time, its scope is so large and the literature so voluminous that no review of this kind can possibly refer to each of the articles published. A great deal of selection has been necessary, and I hope that proper judgment has been exercised. No doubt, however, I have missed a number of important articles and thus failed to give credit to whom it is due. For this I am sorry. Incidentally, this review purports to deal with recent articles only.

HISTORY OF ALLERGY

The history of bronchial asthma and allergy was recently summarized by Stolkind,[1] who laid stress on the antiquity of the disease. Asthma was recognized as a separate disease entity by the early Greeks, "who laid stress on changes in composition of the air, water and food as causes and mentioned the influence of nerves." "The next account of asthma of any importance was compiled by Moses Maimonides"—the Jewish physician to the Sultan, who lived in the twelfth century and four hundred years before such better known writers as van Helmont and Bonetus of the sixteenth and Thomas Willis of the seventeenth century.

BROADENING CONCEPTION OF ALLERGY

Ever since the pioneer work of Walker, Goodale and Cooke twenty years ago, the word "allergy" has connoted the mechanism of hay fever, asthma and eczema—all three being diseases characterized by the urticarial type of reaction as demonstrated when the specific exciting cause

1. Stolkind, E.: The History of Bronchial Asthma and Allergy, Proc. Roy. Soc. Med. **26**:36, 1933.

is scratched or injected into the skin. More recently, other diseases which do not have the wheal and erythemic reaction have nevertheless been referred to as "allergic." Typical, of course, is the tuberculin reaction itself, a response which is delayed and which is inflammatory, but which depends nevertheless on a specific cause, like its immediate prototype. Syphilis and even typhoid fever have been placed in the category of delayed inflammatory skin reactions dependent on a change in the host brought about by the activity of the infectious agent. It was in 1928 that Swift and his associates [2] invoked allergy as a means of explaining the many different cultural findings by as many different students of arthritis, and others have fallen in with his idea. Thus Jenkins [3] and also Rackemann [4] reviewed the evidence for an allergic basis of rheumatism, while Jones and Mote [5] in an important piece of work demonstrated a relation between the immediate and the delayed reaction to streptococci in their rheumatic patients. This will be discussed later in more detail.

Meantime, the factor of change in the host as conceived in the word "allergy" has been utilized in the diagnosis of an increasing number of infectious diseases. New diagnostic methods based on allergy have been applied to a number of infectious diseases. In some of them, the intracutaneous injection of a specific antigen produces a skin reaction of the immediate urticarial type:

Trichinosis.—Augustine and Theiler,[6] in a very complete study, described the development of an inflammatory edema which appears within an hour after the test and may be demonstrated in man as well as in animals some time—at least nine days—after infection. It is elicited by the intradermal injection of an extract of larvae, obtained most easily by peptic digestion of infected muscle. The reaction is sometimes, though not always, accompanied by the finding of precipitins in the circulating blood.

Hookworm Disease.—Vattuone [7] discovered that an antigen prepared from ancylostomas will produce, within from fifteen to thirty minutes after intradermal injection, a clear whitish blister surrounded by a hyperemic circle about 2 cm. in diameter.

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2. Swift, H. F.; Derick, and Hitchcock: Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, Tr. A. Am. Physicians **43**:192, 1928.

3. Jenkins, C. E.: Anaphylactic Basis of Rheumatism, Brit. M. J. **1**:186, 1934.

4. Rackemann, F. M.: The Rôle of Allergy in Arthritis, New England J. Med. **208**:1347, 1933.

5. Jones, T. Duckett, and Mote, John R.: The Phases of Foreign Protein Sensitization in Human Beings, New England J. Med. **210**:120, 1934.

6. Augustine, D. L., and Theiler, Hans: Precipitins and Skin Tests as Aids in Diagnosing Trichinosis, Parasitology **24**:60, 1932.

7. Vattuone, A. B.: New Intradermal Reaction in Ancylostomiasis, M. J. Australia **1**:645, 1933.

Echinococcus Disease.—The Casoni reaction—an immediate urticarial response to the intradermal injection of cyst fluid—should be mentioned because, as previously described by Rackemann and Stevens,[8] it corresponds so closely to the familiar skin reactions to pollens and danders as used in cases of hay fever. Meantime, the purified carbohydrates of the pneumococci also have been shown to produce skin reactions of the immediate urticarial type, which Francis [9] found to have some therapeutic and prognostic importance. Meantime, too, Boor and Miller [10] have been working with carbohydrates purified from the bacterial substance of the gonococcus and of the meningococcus.

The reactions described are all to be classified as immediate responses of the urticarial type. Other newly described reactions are delayed and inflammatory, like the tuberculin reaction.

Undulant Fever.—Undulant fever due to infection with Brucella abortus (Bang) and with the melitensis group of organisms, including the brucella organisms, has been extensively studied by means of skin tests since the new method was described by Burnet [11] in 1922. Burnet used a broth filtrate which he called "melitin." Goldstein [12] reviewed the literature following Burnet's article and described the inflammatory reaction which develops at the site of intradermal injection of a vaccine containing 500,000,000 abortus organisms to the cubic centimeter. He states that a fat-free antigen is preferable, because the vaccine may induce severe local and general reactions. According to Goldstein's tables, the skin test bears no relation to preexisting agglutinins. It is frequently positive when agglutinins are absent. After the skin tests have been made, however, agglutinins rise rapidly in most of the cases. Injection by the intradermal route gives rise to antibodies, as will be discussed later. Brucella vaccine has also been used in cattle to diagnose contagious abortion, the result of the test being entirely comparable with the result of the test with tuberculin.

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8. Rackemann, F. M., and Stevens, A. H.: Skin Tests to Extracts of Echinococcus and Ascaris, J. Immunol. **13**:389, 1927.

9. Francis, Thomas, Jr.: The Value of the Skin Test with Type-Specific Capsular Polysaccharide in the Serum Treatment of Type I Pneumococcus Pneumonia, J. Exper. Med. **57**:617, 1933.

10. Boor, A. K., and Miller, C. Philip: A Study on Bacterial Proteins with Special Consideration of Gonococcus and Meningococcus, J. Exper. Med. **59**:63, 1934.

11. Burnet, E.: Sur un nouveau procédé de diagnostic de la fièvre mediterranéenne, Compt. rend. Soc. de biol. **174**:421, 1922.

12. Goldstein, Jacob D.: Cutaneous Reactions in the Diagnosis of Undulant Fever, J. Clin. Investigation **13**:209, 1934.

Lymphogranuloma Inguinale.—The Frei reaction,[13] described in 1925, is another excellent example of allergy. Cole[14] described the method of making the antigen—essentially an emulsion of infected lymph nodes—and the inflammatory reaction which follows its intradermal injection. His article has a number of striking photographs.

Skin Diseases.—It is, however, in the realm of skin diseases that the broader conception of allergy has developed into practical importance. Another variation in the type of allergic reactions was recognized in 1929 by Bloch[15] when he became interested in his patch tests. Shortly after that, Williams[16] of New York made an important contribution when he discussed the difference between the direct effect of parasites on the skin, which he called "dermatoses," and the indirect effect, which he called "dermatids" and which he interpreted as allergic. This subject will be referred to later.

RELATION BETWEEN VARIOUS PHASES OF ALLERGY

The relation between the various phases of allergy has been recently studied and with great interest and profit. In 1928, Dienes[17] found that when guinea-pigs were treated with intradermal injections of foreign serum or of egg-white, given daily, the responses, if carefully observed, were found to consist at first of a definite red inflammatory reaction appearing within about twenty-four hours after the injection. This delayed reaction appeared within three or four days after the beginning of treatment. Later, however, when the daily injections were continued for eight or ten days, the responses became of the immediate urticarial type and then were found to be accompanied by the development of circulating antibodies in the guinea-pig. In the spring of 1933, Jones and Mote[5] made similar observations on children who for another purpose were given repeated intradermal doses of rabbit peritoneal fluid. Within a few days a reaction of the delayed inflammatory type appeared in these children. Later, however, after about ten days, the intradermal doses were found to produce a reaction of the immediate urticarial type. At about the same time, Simon and Rackemann[18] dis-

13. Frei, Wilhelm: Eine neue Hautreaktion bei "Lymphogranuloma Inguinale," Klin. Wchnschr. **4**:2148, 1925.

14. Cole, H. N.: Lymphogranuloma Inguinale, Fourth Venereal Disease: Its Relation to Stricture of the Rectum, J. A. M. A. **101**:1069 (Sept. 30) 1933.

15. Bloch, Bruno: The Rôle of Idiosyncrasy and Allergy in Dermatology, Arch. Dermat. & Syph. **19**:175 (Feb.) 1929.

16. Williams, C. M.: Enlarging Conception of Dermatophytosis, Arch. Dermat. & Syph. **15**:451 (April) 1927.

17. Dienes, Louis: Further Observations Concerning the Sensitization of Tuberculous Guinea Pigs, J. Immunol. **15**:153, 1928.

18. Simon, F. A., and Rackemann, F. M.: The Development of Hypersensitiveness in Man: I. Following Intradermal Injection of the Antigen, J. Allergy **5**:439, 1934.

covered that repeated doses of guinea-pig serum given intradermally either to so-called allergic patients or to so-called normal persons resulted in the development first of the delayed and later of the immediate type of reaction, the latter being associated with antibodies which could transfer the local skin reaction to the arm of a normal person. It should be noted that this reaction was quite the same in the allergic patients as in the normal controls. As Jones and Mote pointed out, it is evident that these two reactions represent different phases of the response which the normal animal or man exhibits toward repeated intradermal doses.

In a recent article, I [19] yielded to the temptation of suggesting that arthritis and certain other chronic infectious processes represent the early stage of the process of immunity; that hay fever, asthma and eczema represent a later stage (the two diseases are rarely combined in the same patient—which is interesting because both are so common in the community), and that patients continue to have these diseases because they are unable to escape into the final stage called "immunity." They become "stuck" in one or other allergic phase.

Sensitiveness Can Be Artificially Produced in Man.—The experiments of Jones and Mote and of Simon and Rackemann just mentioned have been amplified. Simon [20] has been able to sensitize the nasal mucous membrane so that a second application of a pledget wet with guinea-pig serum and placed in the nose from seven to fourteen days after the first results in a violent attack of symptoms resembling those of hay fever.

These reactions are typical enough, but they are transitory. Further study, as yet incomplete, shows that sensitiveness artificially produced in normal persons tends slowly to disappear; it is not permanent and there is, therefore, grave question whether the behavior of an allergic person does not depend on something more fundamental than a mere quantitative change. The whole question of the influence of heredity in allergy is still pertinent. Not yet can one explain why it is that some people rather than others seem to have the capacity to develop hypersensitiveness and the *Reaktionfähigkeit* which von Pirquet [21] described. The distinction between sensitization and anaphylaxis remains one of the problems in man. Although it is easy to produce sensitiveness of the skin with appearance of reagins in the blood, no clinical picture analogous to that of natural hay fever or asthma has so far been observed. The observations of Simon concern a temporary change only.

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19. Rackemann, F. M.: A Review of the Phases of Allergy, J. Allergy **6**:7, 1934.

20. Simon, F. A.: The Development of Hypersensitiveness in Man: II. Absorption of the Antigen Through the Nasal Mucous Membrane, J. Allergy **5**:451, 1934.

21. von Pirquet, C.: Allergie, München. med. Wchnschr. **53**:1457, 1906.

THE HOST FACTOR IN ALLERGY

The host factor in allergy has been studied to some extent. The differences between allergic patients and normal persons have been investigated from the point of view of physiology and of immunology.

Physiologic Observations.—The physiologic studies are interesting, although it is hard to know whether they indicate results of an allergic process or its cause. Kern and Teller [22] studied the basal metabolism in asthma and eczema, finding frequently a subnormal rate. They felt, however, that their results were an effect and not a cause of the allergic state. At the same time, they estimated the total blood calcium in 75 patients and found it within normal limits in practically all of them. Lierle and Sage [23] reopened the question of the calcium, phosphorus and potassium content of the serum and spinal fluid in asthma. They carefully reviewed the findings of many others, comparing them with their own, and concluded that data on the calcium, phosphorus and potassium of the serum and spinal fluid showed no striking departure from normal values. This paper is important because of the suggestion made originally by Cantarow [24] that the calcium in the spinal fluid is analogous to the diffusible calcium in the blood. Black [25] studied the blood sugar in allergic persons, finding it low, but here again the low level might well have been a cause rather than an effect of the allergic response. One is reminded of Beckman's [26] theory that allergy is a special type of alkalosis amenable to treatment with large doses of acid. On the whole, it is clear that so far, at least, physiologic studies fail to reveal a difference between allergic and normal persons.

Immunologic Observations—The immunologic studies are more important. In 1930, Cohen, Ecker, Breitbart and Rudolph [27] studied the rate of absorption of ragweed pollen blown into the nose. A site in the skin was sensitized passively by an intradermal injection of serum from a ragweed-sensitive patient, and twenty-four hours later ragweed pollen was blown into both nostrils. Within a few minutes an urticarial

22. Kern, R. A., and Teller, Ida: Basal Metabolism and Blood Calcium Studies in Asthma and Allergic Eczema, J. Allergy **2**:488, 1931.

23. Lierle, D. M., and Sage, R. A.: A Study of the Calcium, Phosphorus and Potassium of the Serum and Spinal Fluid in Asthma, J. Allergy **3**:325, 1932.

24. Cantarow, A.: Calcium Studies: V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum, Arch. Int. Med. **44**:667 (Nov.) 1929.

25. Black, J. H.: Blood Sugar in Allergic Persons, J. Texas State Med. **29**:257, 1933.

26. Beckman, Harry: Allergy Considered as a Special Type of Alkalosis, J. Allergy **1**:496, 1930.

27. Cohen, M. B.; Ecker, E. E.; Breitbart, J. R., and Rudolph, J. A.: The Rate of Absorption of Ragweed Pollen Material from the Nose, J. Immunol. **18**: 419, 1930.

wheal appeared at the site of cutaneous sensitization. A comparison of the time of appearance of the wheal in minutes in allergic patients with the time in normal persons showed that the wheal appeared much faster in the nonatopic persons than in the allergic patients. These findings agree closely with those of Brunner and Walzer,[28] who in 1928 found that the response in the sites of passive sensitization of the skin after the ingestion of raw fish was faster in normal persons than in allergic patients. Here attention should be called to the excellent review of the literature on the passage of native proteins through the normal gastro-enteric wall by Ratner and Gruehl.[29] In 1933, Cohen and Rudolph [30] extended their studies and confirmed them in a larger series of patients. In the same article, they described their experiences with histamine, stating that the wheals due to histamine, when excised from the skin and examined microscopically, show smaller reactions in normal, nonatopic persons than in atopic patients. McConnell,[31] working in Alexander's clinic, measured very accurately the size of the wheal produced by the intradermal injection of precise doses of a 1 : 2,000 dilution of histamine, and found that in allergic persons, between attacks, the wheals are smaller, but that during attacks they remain of the same size as in normal persons, and incidentally that this normal size varies considerably from 1.2 to 1.7 sq. cm. Rackemann, Simon and Scully [32] made a similar study, but in place of measuring the wheal obtained with any one dilution, they studied the reaction of their patients and controls to serial dilutions of histamine and found that the differences between normal persons and allergic patients in their response to skin tests with dilutions of histamine were negligible.

The response to typhoid vaccine was studied in the same article, and it was shown that the development of typhoid agglutinins following treatment with typhoid vaccine was essentially the same in a group of 20 patients with asthma as it was in another group of 23 normal nurses in the hospital training school. So far, then, it is not possible to show any particular difference between the immunologic responses of asthmatic patients and normal persons.

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28. Brunner, M., and Walzer, M.: Absorption of Undigested Proteins in Human Beings; Absorption of Unaltered Fish Proteins in Adults, Arch. Int. Med. **42**:172 (Aug.) 1928.

29. Ratner, Bret, and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastro-Enteric Wall, J. Clin. Investigation **13**:517, 1934.

30. Cohen, M. B., and Rudolph, J. A.: Atopic and Bacterial Asthmatic Patients: Some Immunologic and Histologic Evidences of a Fundamental Difference Between Them, J. Allergy **4**:367, 1933.

31. McConnell, F. S.: Observations on the Formation of Wheals: VI. Response of Normal and Allergic Individuals, J. Allergy **4**:177, 1933.

32. Rackemann, F. M.; Simon, F. A., and Scully, M. A.: Further Observations on the Nature of Allergy, J. Allergy **4**:498, 1933.

In the meantime, it is pertinent to recall the work of Woringer,[33] who studied a group of 71 eczematous infants and divided them into two groups. One group he called *holoallergique* because they had antibodies in their blood and also reacted with an urticarial wheal on being tested with egg-white. Some of them also presented urticaria and asthma when egg-white was injected subcutaneously. The other group he called *dermoallergique* because no antibodies could be demonstrated and the sensitiveness was evidently limited to the skin.

Related work is that by Pilcher,[34] who made skin tests on the hairless area over the back of the guinea-pig's neck, using histamine in normal guinea-pigs and horse serum in sensitive animals. The responses in the two experiments were about the same, although the horse serum wheal had a more gradual and chronic development. Its size bore a definite relation to the degree of anaphylactic sensitiveness. The histamine wheal, however, remained the same in the normal and sensitized groups.

Studies of the host factor from a different point of view were started by Goodner,[35] who tried to find out why specific antipneumococcic serum was more active in certain rabbits than in others. The conclusions drawn from an elaborate and interesting series of experiments is that animals which are heavy and have high leukocyte counts are not only more resistant to the infection but are better able to utilize the immune principles passively conferred by immune serum.

CHEMISTRY OF HYPERSENSITIVENESS

The chemistry of hypersensitiveness has received further attention. Landsteiner and van der Scheer,[36] in 1933, prepared new antigens from horse serum and azodyes such that animals prepared with these materials would undergo fatal shock when tested intravenously with solutions of the dyes alone. The chemistry of serum sickness was studied by Jones and Fleisher,[37] who found that the pseudoglobulin was the principle in horse serum most active in causing symptoms. Swineford[38] also found that the globulin fraction was most active. When solutions

33. Woringer, Pierre: L'allergie au blanc d'oeuf chez le nourrisson, Presse méd. **40**:1383, 1932.

34. Pilcher, Lewis S.: The Urticarial Skin Reaction in Normal and Sensitized Guinea Pigs, J. Immunol. **25**:11, 1933.

35. Goodner, Kenneth: Studies in Host Factors in Pneumococcus Infections: I. Certain Factors Involved in the Curative Action of Specific Antipneumococcus Serum in Type I Pneumococcus Dermal Infection in Rabbits; II. The Protective Action of Type I Antipneumococcus Serum in Rabbits, J. Exper. Med. **60**:9, 1934.

36. Landsteiner, K., and van der Scheer, J.: Anaphylactic Shock by Azodyes, J. Exper. Med. **57**:633, 1933.

37. Jones, L. R., and Fleisher, M. S.: Relation of Serum Reaction to Serum Sickness in Rabbits, Proc. Soc. Exper. Biol. & Med. **30**:1195, 1933.

38. Swineford, Oscar: Studies of Anaphylactic Antibody, J. Allergy **5**:265, 1934.

of the globulin in rabbit antihorse serum were treated with increasing quantities of sodium sulphate, the antibody was precipitated quantitatively according to the concentration of the salt. The point of his paper, however, is that the concentrated antibody solution thus obtained was able to protect sensitized guinea-pigs from horse serum shock. The variety of newly identified materials capable of inducing allergy in sensitive persons will be reviewed later in an appendix.

IMMUNOLOGY OF HYPERSENSITIVENESS

Origin of Sensitiveness.—Moll [39] presented new evidence of true occupational asthma, which means in turn that hypersensitiveness may be acquired by the inhalation of foreign dusts. Among a considerable group of patients with occupational asthma, he found 19, or 47 per cent, who were sensitive to sheep wool. This sensitiveness occurred in weavers and menders as well as in workers in a clothing warehouse. Three farmers were sensitive to pollen. Two bakers were sensitive to wheat. Eight handlers of animals and their fur reacted to animal danders. A joiner was sensitive to glue. Two dyers, a seamstress and a surgical nurse were sensitive to the dust of cotton, and three shop assistants were sensitive to house dust. This is further evidence that hypersensitiveness may be acquired. Sensitization by feeding is an important subject which was very carefully reviewed by Ratner and Gruehl [29] in an excellent article giving 86 references. Evidently, it is quite possible to show that native protein can pass unchanged through the normal gastro-enteric wall both in animals and in man. Ross [40] produced immunity in rats by feeding killed cultures of Pneumococcus, type I, by mouth.

Parts Played by Different Tissues.—Different tissues play different parts in the development of hypersensitiveness. It was Bloch [15] who first pointed out that in contact eczema the sensitiveness is of the skin alone and not of any other tissue. Naegeli and his co-workers [41] observed that in cases of drug allergy, notably sensitiveness to antipyrine, certain local areas of the skin became sensitive, and that when the skin over these areas was transplanted to other, normal sites it carried the sensitiveness with it. Wise and Sulzberger [42] likewise worked with surgical skin transplants, but their results were different: When sensitive and normal skin were interchanged and the transplants were allowed to heal,

39. Moll, H. H.: Occupational Asthma with Reference to Wool Sensitivity, Lancet **1**:1340, 1933.

40. Ross, Victor: Immunity in Rats Produced by Feeding the Pneumococcus Type I, J. Immunol. **27**:235, 1934.

41. Naegeli, O.; de Quervain, F., and Stalder, W.: Nachweis des cellulären Sitzes der Allergie beim fixen Antipyrinexanthem, Klin. Wchnschr. **9**:924, 1930.

42. Wise, Fred, and Sulzberger, M. B.: Drug Eruptions: I. Fixed Phenolphthalein Reactions, Arch. Dermat. & Syph. **27**:549 (April) 1933.

the reaction remained in the old sensitive area when the patient took the offending drug; it did not follow the sensitive skin itself.

More recently, Dienes [43] pointed out that the necrotic reactions of the skin are not simply the expression of a high degree of sensitiveness, because they are quite independent of any general sensitiveness, and furthermore, microscopic study shows that the necrosis is limited to the skin itself. Further evidence on the function of the skin was presented by Simon and Rackemann [44] in their work on poison ivy when they showed that guinea-pigs could be made skin-sensitive to Rhus toxicodendron but only when the extract was applied to the skin surface itself; no result followed subcutaneous, intraperitoneal or intravenous injection of poison ivy extract. Meantime, as noted previously, Scon [18] was able to sensitize the skin of guinea-pigs, rabbits and man to various foreign proteins by repeated intradermal injections, producing results with fair regularity. In contrast to this, however, Brunner [45] had no success when, in an analogous experiment, his doses of rabbit epithelium and egg-white were given subcutaneously instead of intradermally. Sensitiveness (as determined by positive skin tests) did not develop in his animals. The last observation is very interesting because it confirms the fact that the skin itself is an organ which has important immunologic functions.

The observations of Stevens [46] are somewhat in line. He made a comparison of pulmonary and dermal sensitivity to inhaled substances, and found that among 45 patients with asthma 11 failed to give a skin reaction to any of 90 different substances, and that these 11 patients also failed to react when tested by inhaling sprays of the specific substances. Thirty-four patients were skin-sensitive. However, of these, only 15 or less than half reacted to inhalant tests, and 9 of the 15 reacted to only one inhalant test. In 39 instances, the skin reaction was strongly positive and yet an attack of asthma resulted from the inhalation of the corresponding extract in only seven instances—a ratio of 1:5. With 53 moderate skin reactions and 76 weak skin reactions, the inhalation test was positive in only 6 and 2 instances, respectively. On the other hand, the skin test was quite negative in 410 instances, and yet asthma followed the inhalation test in 10.

Stevens' study demonstrates that in asthma a marked discrepancy exists between skin tests and inhalant tests. His work is important, for it gives strong support to the clinical observation of a marked dis-

43. Dienes, Louis: The Participation of Cutaneous Epithelium in Immunity Response, J. Immunol. **24**:253, 1933.

44. Simon, F.; Simon, M. G.; Rackemann, F. M., and Dienes, Louis: The Sensitization of Guinea Pigs to Poison Ivy, J. Immunol. **27**:113, 1934.

45. Brunner, Matthew: Active Sensitization in Human Beings, J. Allergy **5**:257, 1934.

46. Stevens, Franklin A.: A Comparison of Pulmonary and Dermal Sensitivity to Inhaled Substances, J. Allergy **5**:285, 1934.

crepancy between positive skin tests and the precise causes of symptoms. It will be referred to again.

No review of tissue sensitiveness can be complete without reference to the extensive and complete studies of Kahn.[47] Having established the method of injecting equal quantities of serial dilutions of a protein like egg-white into the layers of the skin of sensitized rabbits and using the local reactions which develop in a few hours as a measure of sensitiveness, Kahn found that in the case of egg-white the titers of skin sensitivity and serum precipitin are somewhat parallel, but that after a time (from thirty to sixty days) the precipitins fall off while the skin sensitivity remains. Intermediate tests for this sensitivity have perhaps served to maintain it. When the sensitive rabbit is then given an intravenous injection of the protein, desensitization occurs at once; the serum precipitins and the cutaneous sensitivity both fall abruptly. However, the low level is maintained for only a short time (from twenty-four to forty-eight hours), and soon both phenomena reappear, usually in higher titer than before—the precipitins attaining a level somewhat higher than that of the skin sensitivity.

When the same methods are applied to experiments with bacteria (study X), the results are much the same. Repeated intracutaneous injections result in a rapid development of skin reactivity to the suspension of killed organisms used. Serum agglutinins develop, but their titer is low. When, however, the vaccine is given intravenously, the serum agglutinins reach a high point while the skin sensitivity is low. The route of administration is all-important, and the choice of organism used in the experiment makes little difference.

In the bacteria-treated animals, however, desensitization by large doses of killed organisms given intravenously has effects different from those in the protein-treated animals. The skin reaction almost disappears in both groups, but whereas the protein precipitins fall, the serum agglutinins for bacteria maintain their level. Kahn wisely noted that in testing for precipitins the amount of serum used is large while that of protein is small, whereas in testing for agglutinins the amount of serum is small while that of bacteria is large. Perhaps precipitins are absorbed from the circulation more rapidly than agglutinins. However, the desensitized state is brief, and now comes an interesting observation. A few hours after the intravenous dose, the sites of former tests become inflamed, red, purple and finally black with definite necrosis. Still later, the skin sensitivity returns.

From this observation Kahn has drawn an interesting comparison with the chancre of syphilis. According to his theory, the spirochetes invade without resistance until they reach the blood stream. Meantime, the

47. Kahn, Reuben L.: Studies in Tissue Reactions in Immunity, J. Immunol. **25**:295, 1933.

skin has been sensitized, and now the development of circulating antigen results in a sudden desensitization of the skin which is followed quickly by a necrotic reaction. In study XIII, Kahn showed that in rabbits naturally sensitive to certain organisms desensitization by intravenous treatment results in a transient disappearance of skin sensitivity quite as in the sensitized animals. Furthermore, in a short time the sites of tests made before desensitization show a slow development of inflammation which goes on to necrosis as in the treated group of animals.

In the same field is the work of Rich, Jennings and Downing,[48] who inquired: "Is immunity achieved through allergy?" Choosing an organism particularly virulent for rabbits (Pasteurella aviseptica), they produced immunity by giving the vaccine subcutaneously, and then observed the development of large local reactions to their treatment. The animals became sensitized, and some of them were then given large doses of killed bacteria intravenously. Severe symptoms resulted but passed off in most instances. Then the desensitized group of rabbits, the immunized group and a third control group were all given doses of the living organisms intracutaneously. The desensitized animals showed no local reactions up to twenty-four hours. The immune animals displayed a large angry inflammation which in twenty-four hours became necrotic and later discharged pus, with prompt recovery. The controls also showed a large local reaction, but it developed a little more slowly at first, becoming extensive later, with a hemorrhagic ulceration before death, which occurred in less than forty-eight hours. Experiments with pneumococci gave entirely similar results, and incidentally desensitization could be effected by nonspecific means, since animals vaccinated with Past. aviseptica could be desensitized by suspensions of killed pneumococci and vice versa. The point of their experiment was that in the desensitized animals a high immunity could persist in the absence of skin sensitivity and without the development of local inflammation.

This dissociation of allergy and immunity, demonstrated so clearly, is shown also by Kahn's work in which the lack of correlation between the titers of circulating antibody and skin sensitivity is frequently noted. Perhaps one must think of the skin and its sensitiveness as presenting a phenomenon different from anaphylaxis and immunity, but in doing so one must admit that the relation is a close one.

The Eye Can Be Sensitized.—The two Seegals with Khorazo [49] found that when egg-white is injected into the anterior chamber of the rabbit's

48. Rich, A. R.; Jennings, F. B., and Downing, W. M.: Persistence of Immunity After Abolition of Allergy by Desensitization, Bull. Johns Hopkins Hosp. **53**:172, 1933.

49. Seegal, Beatrice C.; Seegal, David, and Khorazo, D.: Local Organ Hypersensitiveness: V. The Fate of Antigen and the Appearance of Antibodies During the Development of Hypersensitiveness in the Rabbit Eye, J. Immunol. **25**:207, 1933.

eye, the eye is sensitized so that later an intravenous dose of the specific substance (egg-white) causes an acute inflammation in it. In another study, the Seegals [50] observed that repeated injections of this protein into the eye result in the development of precipitins, and that when this occurs the egg-white is found to have disappeared from the eye. Irritation of the eye by glycerin followed by intravenous injection of egg-white results in a specific local sensitiveness of the eye. The antigen becomes fixed to the injured tissue so that when, later on, another intravenous dose is given, a specific reaction follows. These experiments remind one of the relation of any infectious process to sensitization. Dienes [51] was the first to show that when egg-white is injected directly into a tuberculous lesion the character and the degree of the resulting sensitiveness are quite different from what they are when the same material is injected into a normal area.

While tissue reactions are of great immunologic importance in the host factor, the behavior of the animal to serums of different kinds is an important item.

Normal vs. Immune Serum.—In 1929, Tuft and Ramsdell [52] observed that whereas normal horse serum is weakly antigenic in the rabbit, immune horse serum is highly antigenic, producing precipitins, positive skin reactions and an anaphylactic antibody in high concentration. In spite of this, however, they found that serum disease as demonstrated by the use of dyes occurred with equal frequency whether normal or immune serum was used. In a recent article, Tuft [53] investigated the question of whether the antibody response might not depend simply on the concentration of the immune serum. By precipitation with ammonium sulphate, he obtained a concentrate 1 cc. of which was equivalent to 12.5 cc. of normal horse serum. The increase in antibodies which followed its use was, however, small. These findings were confirmed by L. R. Jones.[54]

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50. Seegal, Beatrice C., and Seegal, David: Local Organ Hypersensitiveness: VI. An Indirect Method for Its Production in the Rabbit Eye, J. Immunol. **25**:221, 1933.

51. Dienes, Louis: The Immunological Significance of the Tuberculous Tissue, J. Immunol. **15**:141, 1928; Factors Conditioning the Development of the Tuberculin Type of Hypersensitivity, ibid. **23**:11, 1932.

52. Tuft, Louis, and Ramsdell, Susan G.: The Antibody Response in the Human Being After Injection with Normal Horse Serum, J. Exper. Med. **50**:431, 1929.

53. Tuft, Louis: Further Studies in Serum Sickness: IV. Effect of Concentration of Normal Horse Serum upon Antibody Response, J. Immunol. **24**:25, 1933.

54. Jones, L. R.: Skin Sensitivity and Antibody Production upon Administration of Normal and Immune Serum in Rabbits, Proc. Soc. Exper. Biol. & Med. **31**:190, 1933.

Heterologous Serum.—As used in the transfer of anaphylaxis and of immunity, heterologous serum gives rise to a similar problem. Khorazo [55] pointed out that horse serum is more likely than other kinds to produce serum disease in rabbits. Mehlman and Seegal [56] agreed with Avery and Tillett [57] that antipneumococcic serum from the rabbit will passively sensitize a guinea-pig whereas antipneumococcic serum from the horse will not do so. In dogs, however, the horse immune serum will transfer the sensitiveness to the pneumococcic carbohydrate without difficulty. Evidently there is some unknown peculiarity in the two hosts: the guinea-pig and the dog.

Somewhat analogous are the rather complicated observations of Burky.[58] Knowing that an extract of the lens of the eye will react on cataractous persons but not on normal persons, he attempted to sensitize the rabbit to lens protein. Chopped beef lens was incubated in hormone broth, and then the mixture was inoculated with Staphylococcus aureus and allowed to stand for ten days. Rabbits given injections of the filtrate became sensitive so that they would react to the simple lens extract. They were made sensitive to a part of their own tissue. Similarly, rabbits treated with rabbit muscle hormone broth were made sensitive to an extract of rabbit muscle, and the reactions were specific in that the muscle-treated animals would not react to lens any more than the lens-treated animals would react to muscle. Ragweed was used, and Burky observed that ragweed broth toxin also was capable of sensitizing rabbits, causing them to produce precipitins and so changing the animals that they would react later with asthma when placed in an atmosphere of pollen dust. It is important to recognize that Burky's sensitizing doses were given intracutaneously with good results just as Simon and Rackemann had good results in sensitizing man and animals when the doses were given intracutaneously.

DESENSITIZATION

A pertinent editorial [59] in *The Journal of the American Medical Association* for March 3, 1934, quotes Wells in reviewing the four

55. Khorazo, D.: So-Called "Serum Sickness" in Rabbits Following the Intravenous Injection of Various Foreign Serums, J. Immunol. **25**:113, 1933.

56. Mehlman, Julia, and Seegal, Beatrice C.: Passive Sensitization of the Guinea Pig with Rabbit and Horse Antipneumococcus Type I Serum, J. Immunol. **26**:1, 1934; A Comparison of the Sensitizing and the Therapeutic Effect of Rabbit and Horse Antipneumococcus Type I Serum in Albino Mice, ibid. **27**:81, 1934.

57. Avery, O. T., and Tillett, W. S.: Anaphylaxis with the Type-Specific Carbohydrate of Pneumococcus, J. Exper. Med. **49**:251, 1929.

58. Burky, E. L.: The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of Staphylococcus Toxin, J. Allergy **5**:466, 1934.

59. Allergy in Animals, Editorial, J. A. M. A. **102**:694 (March 3) 1934.

ways in which animals become refractory: 1. Desensitization is the exhaustion of antibodies. 2. Antianaphylaxis is a condition of circulating antibodies in excess. 3. Antisensitization is a condition in which the blood has antibodies against the sensitizing serum. 4. Tissue inactivation is a condition in which, through exhaustion or drug action, the sensitized cells cannot respond.

With this summary in mind, the next four papers are of interest. Duthoit [60] threw further light on the advantages of treatment by the intradermal route. Thinking that many intradermal doses are in fact subcutaneous, he dissected a layer of the skin so that he could lift a flap free from the body and in this way demonstrate that his injection could not enter the subcutaneous tissue. By this method, 6 of 16 sensitive animals were successfully protected against anaphylactic shock. Although he [61] showed in the following paper that the duration of the protection was only five days, evidently the exhaustion of antibodies can be accomplished by the intradermal route.

The effect of reticulo-endothelial blockade on the formation of antibodies in rabbits was studied by Tuft,[62] who showed that after injection of an 8 per cent suspension of india ink, whether given intravenously or intraperitoneally, the development of immunity is prevented and the titer of agglutinins, if these are already present, tends to fall. Somewhat similar in effect were the experiments of Hanger,[63] who found that the addition of egg lecithin to fatal doses of serum prevented a fatality in sensitive rabbits. Hanger disclosed that the nature of the protection is unknown, but his work and Tuft's work suggest a fifth mechanism for desensitization, namely, a mechanical blockade of the sources of antibodies.

Meantime, Beckman [64] collected the results of his treatment of patients with hay fever by large doses of acid given by mouth; he reported successful results in 69 per cent of the patients treated by this method as compared with 70 per cent of over 2,000 patients treated by desensitization as reported in the literature. Here is a direct effect on the host factor, but its nature is unknown.

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60. Duthoit, A.: A propos de l'antianaphylaxie par voie intradermique, Compt. rend. Soc. de biol. **112**:384, 1933.

61. Duthoit, A.: Sur la durée de la vaccination antianaphylactique, Compt. rend. Soc. de biol. **112**:385, 1933.

62. Tuft, Louis: The Effect of Reticulo-Endothelial Cell Blockade upon Antibody Formation in Rabbits, J. Immunol. **27**:63, 1934.

63. Hanger, Franklin M.: The Influence of Lipoids in Tissue Immune Reactions, abstr., J. Clin. Investigation **13**:692 (July) 1934.

64. Beckman, H.: Treatment of Hay Fever by Desensitization and with Acid, Lancet **1**:1227, 1933.

BACTERIAL ALLERGY

The delayed, inflammatory, tuberculin type of reaction which is obtained with ordinary bacterial products, with vaccines as well as with so-called bacterial proteins, has already been discussed. Of greater interest is the soluble specific substance, a carbohydrate of the bacterial cell which in specific cases is capable of eliciting an immediate urticarial reaction entirely comparable with the other skin reactions in clinical allergy. The most important recent article on the carbohydrate is that by Avery and Goebel,[65] the pioneers in the whole field, who were able to correlate the observations of others and greatly simplify the whole subject by finding that in the course of isolating the carbohydrate, treatment with dilute alkali results in the removal of the acetyl radical. Another method of extraction avoids the use of alkali and leaves the acetyl in place. The technic is of great importance because the acetyl carbohydrate is antigenic, and when used in the study of immune reactions, it absorbs the specific immune substances. On the other hand, the deacetylated material readily obtained by alkali is nonantigenic. It reacts actively and specifically with immune substances, but it absorbs these substances only in part. The difference between the two is great, but it is easily explained by a small detail in the process of extraction.

An important paper on another subject is that of King [66] on a tuberculin test of value in adults. King found that it is quite possible to standardize the activity of ordinary tuberculin so that a dilution of 1:20,000, for example, becomes the critical dilution which will give positive reactions in patients with active tuberculosis but will not react in normal persons or in those with inactive tuberculous disease. In a series of 225 cases, the results of his skin tests were in accord with the clinical diagnoses in 90 per cent.

THE DIAGNOSIS OF HYPERSENSITIVENESS

This section is limited to the diagnosis of the cause of hay fever, asthma and eczema, which are characterized by an immediate urticarial reaction. Both the scratch method and the intradermal method of skin testing are widely used. O'Keefe and Burgin [67] compared the two, stating that of children with hay fever, 91 per cent gave satisfactory reactions when tested by the scratch method alone. Of children with

65. Avery, O. T., and Goebel, W. F.: Chemoimmunological Studies on the Soluble Specific Substance of Pneumococcus: I. The Isolation and Properties of the Acetyl Polysaccharide of Pneumococcus Type I, J. Exper. Med. **58**:731, 1933.

66. King, Richard B.: A Tuberculin Test of Value in Adults, New England J. Med. **207**:831, 1932.

67. O'Keefe, E. S., and Burgin, L. B.: Comparative Value of Scratch and Intradermal Methods of Skin Testing in Asthma and Hay Fever of Children, New England J. Med. **208**:582, 1933.

asthma, however, only 30 per cent reacted to the scratch test, whereas the intradermal test brought the proportion of positive results up to 87 per cent.

Tuft [68] studied the comparative value of intradermal and ophthalmic tests for sensitiveness to horse serum and concluded that the skin reaction is much more sensitive than the eye reaction and is less disturbing to the patient, especially if the patient is a child. In considering the use of skin tests, I must point out two vital discrepancies in every method. First, skin tests may be positive and yet have no clinical significance. For example, many patients with hay fever react to grass pollens just as strongly as to ragweed and yet have symptoms only in the ragweed season. Second, skin tests may be negative when the patient is sensitive. For example, several children have had symptoms of hay fever in season but have given quite negative reactions to skin tests. They have developed positive reactions later. The theoretical and practical importance of Stevens' [46] demonstrations of pulmonary sensitivity to inhaled substances in the face of negative skin reactions to the corresponding extracts has already been noted.

Patch Test.—This test is new and represents the greatest recent practical advance in the clinical study of allergy. The skin sensitiveness which it represents has been discussed. The use of the test in the diagnosis of contact dermatitis, in which the lesions arise on exposed surfaces because of direct contact with the allergen, as opposed to allergic eczema, in which the cause is blood borne, was discussed by Sulzberger and Wise [69] in a very instructive article in 1931. Any number of substances can be tested, sometimes from 30 to 40 at once, and the test is positive in about 30 per cent of the cases. A more recent article of the same sort is that by Ayres and Anderson,[70] of Los Angeles, who presented good pictures of contact dermatitis and positive patch tests. A case report by Simon and Rackemann [71] illustrates the possibilities of the method. A special use of the patch test is in the diagnosis of obscure dermatids dependent on a sensitiveness to trichophyton infections as described by Sulzberger and Wise.[72] Incidentally, Jadassohn,

68. Tuft, Louis: Comparative Value of Intradermal and Ophthalmic Tests for Sensitiveness to Horse Serum, J. Lab. & Clin. Med. **18**:1160, 1933.

69. Sulzberger, M. B., and Wise, Fred: The Contact or Patch Test in Dermatology, Arch. Dermat. & Syph. **23**:519 (March) 1931.

70. Ayres, S., and Anderson, N. P.: The Patch Test in the Diagnosis of Contact Dermatitis, Ann. Int. Med. **6**:1161, 1933.

71. Simon, F. A., and Rackemann, F. M.: Contact Eczema Due to Clothing, J. A. M. A. **102**:127 (Jan. 13) 1934.

72. Sulzberger, M. B., and Wise, Fred: Ringworm and Trichophytin: Newer Developments, Including Practical and Theoretical Considerations, J. A. M. A. **99**:1759 (Nov. 19) 1932.

Schaaf and Sulzberger [73] were able to demonstrate the sensitiveness of the guinea-pig uterus by the Schultz-Dale technic after treatment of the animal with cultures of Trichophyton.

Urinary Proteose.—A urinary proteose with specific qualities isolated from the urine of patients with asthma and hay fever was described in 1928 by Barber and Oriel.[74] The recent literature on the subject was carefully reviewed by Black and Shelmire,[75] who brought out the fact that in America, at least, the value of the proteose as a specific test has been small and its importance questioned. The chief difficulty seems to be that a similar proteose can be isolated from many clinical conditions other than hay fever and asthma.

Sedimentation Rate.—The rate of sedimentation of red blood cells in uncomplicated hay fever was discussed by Gelfand and Victor,[76] who found that it remains normal before as well as during the season and quite regardless of specific treatment.

Leukopenic Index.—The leukopenic index is a new test devised by Vaughan [77] who checked the observations of the French on *colloidoclasie* and found that the total number of leukocytes does fall after the feeding of certain foods to which the patient is sensitive, and that the degree of fall and the degree of clinical sensitiveness are proportional to each other. The method is of some value in the diagnosis of "food allergy."

Clinical History.—The clinical history, however, remains above all as the best method of identifying the exciting cause of allergic symptoms, and it is surprising that no stress is laid on this important and practical point. The history of an allergic patient should be taken by a detective rather than by a doctor! It should express the time of events, of changes in symptoms for better or worse, of changes in residence or of occupation by *exact dates.* The season of the year, school vacations, travel and admissions to the hospital, when correlated with symptoms, will frequently reveal the cause of the trouble. It is important to account for all the time in an effort to explain not only when and why the attack of asthma, eczema or migraine began, but also when and why it ended. If the history is taken properly and carefully, skin tests will become almost unnecessary, and their chief function will be

73. Jadassohn, W.; Schaaf, F., and Sulzberger, M. B.: Der Schultz-Dalesche Versuch mit Trichophyton, Klin. Wchnschr. **11**:857, 1932.

74. Barber, H. W., and Oriel, G. H.: A Clinical and Biological Study of Allergy, Lancet **2**:1064, 1928.

75. Black, J. H., and Shelmire, B.: The Urinary Proteose in Allergy, J. Allergy **5**:373, 1934.

76. Gelfand, B. B., and Victor, G.: The Sedimentation Rate in Hay Fever, J. Allergy **5**:583, 1934.

77. Vaughan, W. T.: Food Allergens: The Leucopenic Index. Preliminary Report, J. Allergy **5**:601, 1934.

to confirm the history and determine the degree of sensitiveness before the start of specific treatment.

SEVERAL DIFFERENT CLINICAL MANIFESTATIONS OF ALLERGY

The separate discussion of hay fever, asthma, eczema and allied conditions is beyond the scope of a review of this kind. Perhaps they can be considered at a later time. There are, however, a number of topics which demand attention even in this limited space.

Drug Allergy.—The allergy caused by ingestion of a drug is receiving attention and will receive more of it. The discovery by Madison and Squier [78] that primary agranulocytopenia is often due to a peculiar susceptibility to certain drugs, notably amidopyrine (they described the reaction as an allergic or anaphylactoid reaction), has led to a considerable discussion of the use and abuse of all the new sedative drugs and has drawn new attention to drug allergy. The recent papers by Short and Bauer [79] on cinchophen, Ford [80] on quinine, Meredith [81] on barbital derivatives and Scheer and Keil [82] on codeine are typical.

Sensitiveness to Tobacco.—This condition has a rather special interest because Harkavy [83] of Mount Sinai Hospital presented evidence to show that sensitivity to tobacco may have an important bearing in the etiology of thrombo-angiitis obliterans and other vascular diseases. He finds that patients with these diseases show good skin reactions to tobacco whereas normal persons used as controls yield mostly negative reactions. Sulzberger [84] confirmed this work. His findings are of some interest. Intradermal tests with tobacco extracts produced immediate urticarial wheals in 36 per cent of smokers and in only 16 per cent of nonsmokers. Among adults with heart disease and in the general hospital population, the figures are 26 per cent and 28 per cent, respectively. On the other hand, of 13 patients with thrombo-angiitis obliterans 10, or 77 per cent, showed positive reactions. In a more recent article,

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78. Madison, F. W., and Squier, T. L.: Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**:755 (March 10) 1934.

79. Short, C. L., and Bauer, W.: Cinchophen Hypersensitiveness: A Report of Four Cases and a Review, Ann. Int. Med. **6**:1449, 1933.

80. Ford, William K.: Drug Eruption Due to Quinine: Recurrence Following Use of Contraceptive, J. A. M. A. **103**:483 (Aug. 18) 1934.

81. Meredith, Florence L.: Reactions to Certain Barbital Derivatives, J. A. M. A. **102**:2099 (June 23) 1934.

82. Scheer, M., and Keil, H.: Skin Eruptions Due to Codeine, J. A. M. A. **102**:908 (March 24) 1934.

83. Harkavy, J.: Tobacco Sensitiveness in Thromboangiitis Obliterans, Migrating Phlebitis and Coronary Artery Disease, Bull. New York Acad. Med. **9**:318, 1933.

84. Sulzberger, M. B.: Studies in Tobacco Hypersensitivity, J. Immunol. **24**:85, 1933.

Harkavy [85] presented the results of tests with the different kinds of tobacco extracts—Burly, Virginia and others.

Unusual Manifestations of Allergy.—First of all, Vaughan [86] urged that one distinguish between major and minor allergic manifestations. According to his figures, 10 per cent of the population have major allergy and are usually found sensitive to the more common or staple allergens. In contrast to this, he found that as many as 50 per cent gave a history of minor episodes which closely simulated more typical allergic manifestations. Transient eruptions of the skin, headache and gastro-intestinal disturbances of atypical character and occurring with considerable frequency, he found to depend on a sensitiveness, not to the staple allergens, but to the occasional and odd allergens. Routine tests made on patients of this sort show a surprising incidence of queer reactions difficult to interpret on any other basis than that of minor allergy. The differences between the two groups are in his opinion more quantitative than qualitative. This work must be correlated with recent observations which my associates and I have made on skin tests in normal persons—that positive skin reactions are by no means uncommon even when no allergy of any kind is suspected.

Migraine.—This disorder has not received its customary attention from the allergic point of view during the past year. In a special article, Bassoe [87] reviewed the subject from every angle and discussed the whole problem in a scholarly manner. Only half of one of his eleven columns is devoted to allergy as an important etiologic principle.

Epilepsy.—This condition has been mentioned as of allergic origin. Adamson and Sellers [88] found that the skin tests were positive in 30 per cent of 100 cases but that the transference of the skin reactions to the skin of normal persons was successful in only 10 of the cases, and even in these, it was not possible to show any clinical relation between the attacks and the particular foreign substance.

Gastro-Intestinal Allergy.—This is another favored topic, important chiefly because the attack of gastro-intestinal allergy frequently simulates a surgical emergency and then leads to operation. Such a case was reported by Gallison,[89] who emphasized the importance of an eosinophilia

85. Harkavy, J.: Skin Reactions to Tobacco Antigens in Smokers and Non-Smokers, J. Allergy **5**:131, 1934.

86. Vaughan, W. T.: Minor Allergy: Distribution, Clinical Aspects and Significance, J. Allergy **5**:184, 1934.

87. Bassoe, Peter: Migraine, J. A. M. A. **101**:599 (Aug. 19) 1933.

88. Adamson, W. B., and Sellers, E. D.: Observations on the Incidence of the Hypersensitive State in One Hundred Cases of Epilepsy, J. Allergy **4**:315, 1933.

89. Gallison, D. T.: Gastro-Intestinal Allergy as a Cause of Intestinal Obstruction, New England J. Med. **211**:164, 1934.

of 8 per cent and the greater importance of the prompt and dramatic relief from all the symptoms following a hypodermic injection of epinephrine.

Cold Allergy.—Allergy due to cold is rare, but Paul [90] has demonstrated another typical case in which local urticaria was shown on application of cold water.

Arthus Phenomenon in Man.—This observation is rare, and the case reported by Ross [91] is of some interest. A small boy had been given diphtheritic toxin-antitoxin for immunization. A year later, he received tetanic antitoxin for an injury of the scalp. Three days later, a temperature of 104 F. developed, and the symptoms so resembled scarlet fever that he was given an additional treatment with streptococcic antitoxin, injected into the buttock. Immediately, the site of injection became indurated and inflamed, and the lesion developed with such fulminating intensity that five days later the entire thigh, hip and abdomen were involved in a huge necrotic sloughing mass. The boy died that evening, nine days after the injection of the tetanic antitoxin.

Anaphylactic Shock.—Incidentally, Waldbott [92] recently made a study of nine fatal cases of anaphylactic shock, in the last of which ragweed was the cause, the patient dying within two hours after the last dose of ragweed extract. Waldbott and Ascher,[93] too, drew attention to what they call an "unusual reaction simulating allergic shock." This patient also was under treatment with ragweed and for no particular reason was seized with paroxysms of coughing, dyspnea and yawning following each of the doses. Later these symptoms became so severe that it was decided to dispense with the treatment. At that time, however, it was found that the injection of physiologic solution of sodium chloride without the patient's knowledge would produce the same clinical picture. As Waldbott stated, this case offers an excellent demonstration of the fact that attacks of "asthma nervosum" may be practically identical with those of allergic asthma.

TREATMENT OF HAY FEVER

The treatment of hay fever must depend primarily on an accurate knowledge of the pollens in the particular district. The American

90. Paul, Lee W.: Cold Allergy, J. A. M. A. **103**:24 (July 7) 1934.

91. Ross, Fred E.: The Arthus Phenomenon: Report of a Case, J. A. M. A. **103**:563 (Aug. 25) 1934.

92. Waldbott, George L.: The Prevention of Anaphylactic Shock with a Study of Nine Fatal Cases, J. A. M. A. **98**:446 (Feb. 6) 1932.

93. Waldbott, George L., and Ascher, M. S.: Unusual "Reaction" Simulating Allergic Shock, J. A. M. A. **102**:127 (Jan. 13) 1934.

Association for the Study of Allergy is fortunate to have the services of Mr. O. C. Durham available to its members. His work is good. In 1933, he gave information about the plants of Canada [94] and of Chicago [95] that cause hay fever and added [96] an interesting discussion of those pollens which may overlap into the neighboring districts to complicate the local pollen incidence.

From the Southwest, Lamson and Watry [97] described the sages, thistles and junipers which cause hay fever in northern Arizona.

The treatment of hay fever is by elimination and by desensitization particularly.

Air Filtration.—This measure and air conditioning have suggested various studies. Gay [98] of Johns Hopkins University, with the cooperation of the General Motors Corporation, has been able to work with a very efficient room "air conditioned" with frigidaire.

Nelson, Rappaport and Welker [99] had a similar opportunity in Chicago, and Vaughan and Cooley [100] have used the method in Richmond. These studies seem to show that patients with hay fever vary considerably in their response to cool and dust-free air. Some of them lose their symptoms in a few minutes; others, however, require from one to two hours before relief comes. On going back to the outer world, symptoms may return promptly, or the patient may be comfortable for a time, usually a few hours, but the time is not long, and the symptoms are prone to recur. The original hope that if the patient could return to the air-conditioned room each night and be outside of it for only from eight to ten hours a day he would remain relatively free from symptoms is not sustained. Such an intermittent residence in the ward will not prevent hay fever.

Desensitization or Specific Treatment.—This treatment in hay fever varies in technic according to the number of doses and the time between

94. Durham, O. C.: Fall Hay Fever Pollens of Canada, Canad. M. A. J. **28**:604, 1933.

95. Feinberg, S. M., and Durham, O. C.: Hay Fever in Chicago and Suburbs: Clinical, Field, and Air Observations, Illinois M. J. **63**:464, 1933.

96. Durham, O. C.: Complicating Pollen Factors Encountered in Ragweed Hay Fever; An Atmospheric Study, J. A. M. A. **100**:1846 (June 10) 1933.

97. Lamson, R. W., and Watry, A.: Survey of a Botanic Oasis in the Desert of Northern Arizona, J. Allergy **5**:389, 1934.

98. Gay, L. N.: The Treatment of Hay Fever and Pollen Asthma by Air-Conditioned Atmosphere, J. A. M. A. **100**:1382 (May 6) 1933.

99. Nelson, T.; Rappaport, B. Z., and Welker, W. H.: The Effect of Air Filtration in Hay Fever and Pollen Asthma: Further Studies, J. A .M. A. **100**: 1385 (May 6) 1933.

100. Vaughan, W. T., and Cooley, L. E.: Air Conditioning as a Means of Removing Pollen and Other Particulate Matter and of Relieving Pollenosis, J. Allergy **5**:37, 1933.

them as well as according to the route by which the doses are given. The question of perennial versus preseasonal treatment has been debated extensively. A good survey of the literature is by Unger,[101] who added the figures on his own results to show that results are infinitely better with the perennial than with the preseasonal method. The route by which the doses should be given is an interesting problem in view of the work of Kahn,[47] referred to in the discussion on desensitization. Phillips[102] reported that he gave his patients doses every day and injected all of them intradermally, saying that an average series of 14 doses was quite sufficient to obtain striking relief in a large proportion of the cases. This is interesting because in animal experiments repeated intradermal doses increase the sensitiveness of the skin. Theoretically, desensitization should be obtained best by treatment which is given intravenously. This would be the method of choice if the main object were to produce a true immunity. Lichtenstein[103] tried the method and treated 6 patients, all sensitive to ragweed; with intravenous doses of various dilutions, the exact amount being made up to about 15 cc. with salt solution. His patients were given from 1 to 15 treatments. Every patient had one or more reactions varying in character, but all of them did well. The fact is interesting and the idea needs further consideration.

The latest treatment for hay fever is that reported by Warwick,[104] who employs nasal ionization using a metallic electrode and salts of the same metals. He precipitates the metal on the nasal mucous membrane by means of a suitable direct current. He made the claim that no damage is done to the nose, and that after a slight reaction the patients are better of their hay fever and are rendered less susceptible to head colds later on. The method is being used in many clinics at the present time.

Pollen Treatment.—The results of this treatment may often be reflected by a reduction in the size of skin reactions, according to Colmes and Rackemann,[105] but the rule is not absolute, for good results occurred without change in the size of the skin reactions in 18 per cent of their cases, and poor results occurred in 11 per cent in spite of the fact that in this group the skin reactions were smaller after the treat-

101. Unger, L.: Perennial Versus Preseasonal Treatment of Hay Fever, J. Allergy **3**:531, 1932.

102. Phillips, E. W.: Intradermal Pollen Therapy During the Attack, J. Allergy **5**:29, 1933.

103. Lichtenstein, M. R.: Intravenous Pollen Therapy, J. Allergy **5**:230, 1934.

104. Warwick, H. L.: Desensitization of Nasal Mucous Membranes for Relief of Hay Fever, Asthma and Food Allergy, Laryngoscope **44**:173, 1934.

105. Colmes, A., and Rackemann, F. M.: Further Observations on the Changes in Skin Tests Following Specific Pollen Therapy, J. Allergy **4**:473, 1933.

ment than before. It seems that relief from symptoms and reduction in reactions could hardly depend on a common basis. Markow and Spain [106] had a similar experience, although they reported that a diminution in the size of skin reactions did not occur in many of their cases and that when it did, it was seen only after several years of treatment.

Clinical End-Results.—Feinberg [107] was wise in urging that the experiences of the individual patient be compared with those of the particular group to which the patient belongs, for, as he pointed out, the severity of the pollen season changes from year to year, and the results of treatment in any one case must be interpreted according to this general change.

Walker [108] expressed the belief that hay fever is curable. Of his total of 734 patients, 190, or 26 per cent, had remained free from symptoms for three years or over. His figures show that each succeeding year of preseasonal treatment increases the chance of a permanent result.

STUDIES IN ASTHMA

Studies in asthma are numerous. The most important recent progress concerns the relation of lesions of the nose and throat to asthma. There are three excellent papers. Kern and Schenck's [109] paper contains an excellent review of the preceding literature. Their work concerns mucous polyps, which they found to be extremely common in allergic conditions but comparatively rare in patients with nonallergic diseases, even in those patients who have extensive and chronic sinus infection. In their experience, all patients with mucous polyps have a personal history of allergy, and they declared that the finding of mucous polyps warrants the assumption that the patient is of allergic strain and should be studied from the standard of clinical hypersensitiveness.

Grove and Cooke [110] studied the cultures and tissues taken at operation from patients with chronic hyperplastic sinusitis. Eosinophilic infiltration was the rule, and organisms were present in 85 per cent of their specimens. In their experience, it is unusual to find polypi or even

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106. Markow, H., and Spain, W. C.: The Effect of Consecutive Years of Treatment upon Cutaneous Sensitiveness in Late Hay Fever, J. Allergy **4**:363, 1933.

107. Feinberg, Samuel M.: A Method of Evaluation of Results in Hay Fever; Its Application to Certain Modes of Treatment, Ann. Int. Med. **6**:1153, 1933.

108. Walker, I. C.: Curability of Hay Fever, Arch. Int. Med. **54**:289 (Aug.) 1934.

109. Kern, R. A., and Schenck, H. P.: Allergy a Constant Factor in the Etiology of So-Called Mucous Nasal Polyp, J. Allergy **4**:485, 1933.

110. Grove, R. C., and Cooke, R. A.: Etiology and Nature of Chronic Hyperplastic Sinusitis, Arch. Otolaryng. **18**:622 (Nov.) 1933.

chronic thickening of the sinus membrane without a complicating infectious process. Of 175 patients with infective allergy, 48 per cent showed definite polyp formation. It is in some of these patients that vaccines produce violent constitutional reactions.

Weille [111] operated on 40 patients with asthma who suffered from chronic sinus disease, and he followed all of them very carefully for at least a year and some of them for five or six years. Following operation, temporary cure was common, but permanent cure occurred in only 5 of the 40 cases, with 9 in which the condition was markedly improved. Weille stated that patients with polyp formation or with purulent cystic degeneration are the most favorable for operation, whereas those with purely extrinsic causes, whose asthma depends on hypersensitiveness to foods or dusts, receive no benefit from surgical intervention. Somewhat paradoxical is his observation of several patients who were relieved of their asthma as well as of their sinusitis even though only one side of the nose was operated on. Another paradox was the finding that operation caused a marked improvement in the nasal condition but did not affect the asthma. Knowledge of the relation of chronic infection to asthma is still faulty, but physicians are learning.

At the end of this survey, I should like to call attention once more to what I believe are the fundamental problems in allergy. First, the function and the purpose of the allergic reaction must be understood. Evidence has been presented to show that it represents a phase of the process of immunity. It is obvious that if the mechanism could be understood accurately, the treatment of hay fever, for example, would be understood and then the results would always be satisfactory. A second problem concerns the so-called allergic or atopic state: whether those patients whom one regards as "typically allergic" are really different from normal persons or whether the apparent variations depend merely on a quantitative change. A third problem concerns the mechanism of the production of symptoms, as, for example, in asthma of the severe, intractable type. Is there an excess of some poisonous substance or is there, perhaps, a lack of some protective mechanism which is present in normal persons? It is to be hoped that the investigations to be described during the coming year will help in the solution of these problems.

Meantime, the substances found to elicit one or other symptoms of allergy are in great and increasing variety. The following list of references to new allergens will indicate the scope of the subject and will show why the list of possibilities can never be closed.

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111. Weille, Francis L.: Studies in Asthma: XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, J. A. M. A. **100**:241 (Jan. 28) 1933.

REFERENCES TO NEW ALLERGENS

The offending substance caused allergy of the immediate atopic type and gave urticarial skin reactions.

Adkinson and Walker, I. C.: A Patient Sensitized to an Art Gum Eraser, J. A. M. A. **101**:2117 (Dec. 30) 1933.

Baagøe, K.: Mehlidiosynkrasie als Ursache von vasomotorischer Rhinitis und Asthma, Ugesk. f. læger **95**:513, 1933.

Bennett, Richard H., and Schwartz, Emanuel: Castor Bean Dust Sensitization, J. Allergy **5**:427, 1934.

Duke, W. W.: Sensitiveness to Corn Shuck, J. A. M. A. **99**:468 (Aug. 6) 1932.

Feinberg, S. M.: Pyrethrum Sensitization, J. A .M. A. **102**:1557 (May 12) 1934.

——and Aries, P. L.: Asthma from Food Odors, J. A. M. A. **99**:2280 (June 25) 1932.

Hollander, Lester: Urticaria Due to Senna Leaves, J. A. M. A. **100**:1329 (April 29) 1933.

Idiosyncrasy to Quinine, Queries and Minor Notes, J. A. M. A. **101**:731 (Aug. 26) 1933.

Parlato, S. J.: Emanations of Flies as Exciting Causes of Allergic Coryza and Asthma, J. Allergy **3**:459, 1932.

——LaDuca, P. J., and Durham, O. C.: Studies of Hypersensitiveness to the Emanations of the Caddis Fly (Trichoptera), Ann. Int. Med. **7**:1420, 1934.

Randolph, Howell: Allergic Response to Dust of Insect Origin, J. A. M. A. **103**:560 (Aug. 25) 1934.

Taub, Samuel J.: Allergy Due to Silk, J. Allergy **1**:539, 1930.
Cottonseed Allergy, J. A. M. A. **103**:334 (Aug. 4) 1934.

The offending substance caused immediate symptoms, but skin tests were either negative or were not made.

Allergic Reaction to Honey, Queries and Minor Notes, J. A. M. A. **101**:728 (Aug. 26) 1933.

Lamson, R. W., and Thomas, R.: Some Untoward Effects of Acetyl-Salicylic Acid, J. A. M. A. **99**:107 (July 9) 1932.

Spielman, A. D., and Baldwin, H. S.: Atopy to Gum Arabic (Causing Asthma), J. A. M. A. **101**:444 (Aug. 5) 1933.

Watson, S. H., and Kibler, S. C.: [Chlorine in] Drinking Water as a Cause of Asthma, J. Allergy **5**:197, 1934.

The offending substance caused a dermatitis and gave a positive patch test.

Cummer, Clyde L.: Dermatitis from the Use of Hexylresorcinol Solution, S.T. 37; Acquired Sensitivity, J. A. M. A. **100**:884 (March 25) 1933.

Downing, J. G.: Dermatitis from Rubber Gloves, New England J. Med. **208**:196, 1933.

Eades, M. F.: Dermatitis of the Breasts Caused by Compound Tincture of Benzoin: Report of Three Cases, New England J. Med. **211**:632, 1934.

Fowlkes, R. W.: Dermatitis Due to Nupercaine, J. A. M. A. **100**:1171 (April 15) 1933.

Fox, Howard: Nickel Dermatitis from Spectacle Frames and Wrist Watch, J. A. M. A. **101**:1066 (Sept. 30) 1933.

French, S. W.: A Case of Skin Sensitivity to Parthenium Hysterophorus, Mil. Surgeon **66**:623 (May) 1930.

Grant, L. R.: Flaxseed Sensitization with Review of Literature, J. Allergy **3**:469, 1932.

Henry, S. A.: Celery Itch: Dermatitis Due to Celery in Vegetable Canning, Brit. J. Dermat. **45**:301, 1933.

Hollander, Lester: Dermatitis of the Upper Eyelids Due to the Use of a "Hair Tonic" (Wildroot), J. A. M. A. **97**:1384 (Nov. 7) 1931.

Levin, Oscar L.: Sawdust Dermatitis, J. A. M. A. **100**:570 (Feb. 25) 1933.

Senear, Francis E.: Dermatitis Due to Woods, J. A. M. A. **101**:1527 (Nov. 11) 1933.

Sulzberger, M. B., and Weinberg, C. B.: Dermatitis Due to Insect Powder, J. A. M. A. **95**:111 (July 12) 1930.

The offending substance caused severe dermatitis, but patch tests were negative.

Baer, Harry L.: A Dermatitis Due to Aniline Dye in a Food Product, J. A. M. A. **103**:10 (July 7) 1934.

Langenbach, Alfred, M.: Acquired Sensitization to Sodium Iso-Amylethylbarbiturate (Sodium Amytal) as Evidenced by Cutaneous Eruptions: Report of 4 Cases, J. A. M. A. **102**:1376 (April 28) 1934.

Matzger, Edward: Can Sensitivity to Dinitrophenol Be Determined by Skin Tests? J. A. M. A. **103**:253 (July 28) 1934.

263 Beacon Street, Boston.

News and Comment

ATLANTIC CITY SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Section on Practice of Medicine of the American Medical Association has appointed the following section exhibit committee for the Scientific Exhibit at the Atlantic City session of the American Medical Association and the Canadian Medical Association: Irving S. Wright, New York, chairman; Russell L. Haden, Cleveland; Eugene S. Kilgore, San Francisco; L. G. Rowntree, Philadelphia, and D. Sclater Lewis, Montreal, Canada. Application for space must be made by Feb. 25, 1935. Application blanks may be obtained from any of the members of the committee or from the Director, Scientific Exhibit, 535 North Dearborn Street, Chicago.

ACADEMIA NACIONAL DE MEDICINA DE MEXICO

The following officers of the Academia Nacional de Medicina de Mexico were recently elected: Dr. Francisco de P. Miranda, president; Dr. Gustavo Baz, vice-president; Dr. Alfonso Pruneda, permanent secretary; Dr. Miguel E. Bustamante, annual secretary, and Dr. Ramón Pardo, treasurer.

Book Reviews

A Textbook of Histology: Functional Significance of Cells and Intercellular Substances. By E. V. Cowdry, Professor of Cytology, Washington University School of Medicine. Price, $5.50. Pp. 503, with 242 illustrations. Philadelphia: Lea & Febiger, 1934.

Departing from the conventional approach in the didactics of histology, Cowdry builds up the subject with the vascular system as a central theme. The first chapter is devoted to an introductory consideration of the body fluids—tissue fluid, blood and lymph—touching on the physiologic import of these mediums. Cowdry then proceeds with a detailed discussion of blood (sixty-three pages), followed by separate chapters on the blood vessels and the heart, the whole being emphasized as a "principal integrator" system. Lymphatic vessels and the chief lymphoid organs are next considered, with a view to their functional relationships with this integrator system; the endocrines are next discussed as agents of "chemical integration." The digestive system is likewise alined with the vascular mechanism, as a provision for the "intake of water, nutriment, accessory food factors and removal of waste." The respiratory system is as naturally emphasized for its rôle in "oxygen consumption and carbon dioxide elimination," and the urinary system is discussed as the agent for "regulation of constitution of blood and removal of waste." The nervous system is contrasted with the vascular system in mediating "rapid integration." The next chapters consider the connective and muscular systems as the means of "architectural support" and the reproductive system for "perpetuation of the race," concluding with a consideration of the skin, which serves for "unification, protection and adjustment." As these headings indicate, the treatment is distinctively physiologic throughout, and a direct, lively style adds forcefulness and interest. The book may be recommended to those who desire a reference work on modern physiologic histology more compact than the three-volume "Special Cytology" edited by the same author. In keeping with his plan, Cowdry has not followed the tradition of proceeding successively from cell structures to systematic description of elementary tissues, organs and systems. He has omitted figures which would only "show at a glance what the actual preparations will lead the students to discover for themselves," with the result that but few illustrations of routine histologic sections appear. Favorably impressed as they may be by the vivification of histology afforded by this book, some teachers of the subject will doubtless consider it ill-adapted in other respects as a text for the average beginning medical student.

Tuberculosis in the Child and the Adult. By Francis Marion Pottenger, A.M., M.D., LL.D., F.A.C.P. Price, $8.50. Pp. 611, with 85 illustrations. St. Louis: C. V. Mosby Company, 1934.

This excellent monograph represents the recording of the experiences and the studies of many years of a well known specialist in the field of pulmonary tuberculosis. The occurrence of tuberculosis in childhood and the subsequent relation that this disease bears to tuberculosis in adults is clearly presented. A detailed discussion is given of the body's reaction to the tubercle bacillus in respect to cell sensitization and immunity. The effects of reinoculation on the mechanism of immunity are emphasized, and it is shown that the clincal picture varies according to the several immunity reactions.

The mechanism of symptoms is explained on a visceroneurologic basis. Pottenger has divided the symptoms into three groups: those due to toxemia, those due to reflex stimulation and those due to the tuberculous process per se. The diagnosis of tuberculosis is given thorough consideration, with a careful

appraisal of each diagnostic procedure. The various types of tuberculosis are illustrated by roentgenograms. The author emphasizes the advantages of the dilution-flotation-trinitrophenol method over the usual methods of examining for tubercle bacilli.

The complications of the disease are discussed in a thorough manner as regards the diagnosis, prognosis and treatment.

The principles of treatment are comprehensively presented. It is suggested that the technic in the employment of therapeutic measures be comparable to that in surgical procedures. The importance of tuberculin in treatment is convincingly brought out. A thorough and practical discussion is given on the indications, contraindications and results of the various forms of compression therapy.

The latter part of the book is devoted to diagnostic and therapeutic principles, with reports of illustrative cases and roentgenograms.

This book should be a gratifying addition to any student's or physician's library.

The Harvey Lectures, 1932-1933. Pp. 233. Baltimore: The Williams & Wilkins Company, 1934.

This volume, issued by the Harvey Society, contains a number of significant lectures constituting reviews of important subjects in chemical and metabolic phases of medicine. Dr. Julius Bauer, professor of clinical medicine of the University of Vienna, contributes a review, "The Constitutional Principle in Clinical Medicine." Dr. L. O. Funkel, a member of the department of animal and plant pathology of the Rockefeller Institute for Medical Research, describes "The Similarities Between the Diseases of the Vegetable Kingdom and Those of Man and Animals." Dr. George W. Corner, professor of anatomy of the University of Rochester, reviews the recent interesting evidence regarding "The Nature of the Menstrual Cycle." Then follows a seventy page paper by Dr. Harvey Cushing, "Dyspituitarism: Twenty Years Later." In this he gives particular attention to the syndrome which he now calls pituitary basophilism. Following is a lecture by Dr. James B. Conant, professor of chemistry, Harvard University, "The Oxidation of Hemoglobin and Other Respiratory Pigments." This is followed by "Contributions of Chemistry to the Knowledge of Immune Processes" by Dr. Michael Heidelberger, associate professor of biologic chemistry, Columbia University. Then there is a discussion, "Recent Biochemical Studies of Liver Function," by Dr. J. C. Drummond, professor of physiology and biochemistry, University College, London. The volume is completed by a lecture "Humoral Transmission of Nervous Impulses" by Dr. Otto Loewi, professor of pharmacology, the University of Graz, Austria, the pioneer in this field through his discovery of the so-called *Vagusstoff*.

A careful perusal of this volume will prove very much worth while to every physician attempting to keep abreast in this important humoral field of internal medicine.

L'Infarctus du myocarde: Etude expérimentale, électrocardiographique, et clinique. By Eduardo Coelho, Professeur à la Faculté de Médecine, Médecin de l'Hôpital de Santa Marta, Lisbonne. Paper. Price, 35 francs. Pp. 212, with 105 figures and illustrations. Paris: Masson & Cie, 1934.

This work shows the result of careful and painstaking observation on the effect of obstruction of the coronary circulation. The subject is considered from the experimental and clinical sides, is well treated, succinctly set forth and accompanied by a fairly comprehensive bibliography.

The first portion of the book is devoted to a review of the anatomy of the coronary circulation. Diagrams and photographs assist the reader in visualizing this.

In the experimental production of coronary occlusion several methods were used. Ligature, before and after section of the vagus and sympathetic nerves, was employed to obstruct various branches of the coronary arteries. Infarction was

produced in numerous places by the use of alcohol and silver nitrate, and, lastly, embolic infarction was caused by iodized poppy-seed oil 40 per cent, charcoal and lycopodium powder.

The immediate and ultimate effect of these procedures is discussed in relation to the electrocardiogram and to the mortality in experimental animals.

The clinical consideration of coronary occlusion is developed by a discussion of twenty-eight cases, with observations at autopsy, and these are correlated with the experimental work. Electrocardiograms are shown or described in all the cases.

Finally, the clinical cases are tabulated in relation to the common clinical symptoms and findings in this disorder.

Die Zuckerkrankheit. By Ferdinand Bertram. Price, 5.80 marks. Pp. 94, with 15 illustrations. Leipzig: Georg Thieme, 1934.

After reviewing in a reasonably satisfactory and brief manner the current views on the pathogenesis of diabetes, Bertram proceeds to outline the method of treatment found effective in the Hamburg clinic. The dietary measures described will not be very useful for the American practitioner. They are complicated, as compared with American plans, and the type of foods called for and the frequent meals are foreign to American food habits.

Bertram's strenuous objection to the patient's testing his urine leaves the reviewer with the impression that the very corner-stone of good treatment is neglected in Hamburg. With no knowledge by the patient of the state of his urine, it becomes almost impossible for him to regulate his dose of insulin. The objection is based on the fear that the patient will be disturbed psychologically if he is constantly watching his urine, but this is seldom found to be the case in the larger American clinics. Bertram prefers to have his patients excrete sugar in amounts of at least from 10 to 20 Gm. daily. He maintains that the majority of them feel healthier under such circumstances. The reviewer disagrees with this. It is admitted that overly rigid treatment, such as may be required to bring the blood sugar to a normal level, is to be avoided, especially in cases complicated with arteriosclerosis. The danger of insulin treatment in patients with heart disease, especially with hypertension and coronary sclerosis, must not be minimized, but it is not as serious, in the reviewer's opinion, as is suggested by this book. The reviewer has seen a few cases in which anginal pain could be produced by overrigid treatment, but careful inquiries as to the experience of the larger American clinics in this matter has revealed very few deaths attributable to this cause.

Clinical Pathology of the Jaws. By Kurt H. Thoma, D.M.D., Professor of Oral Pathology in Harvard University. Price, $9. Pp. 643, with 423 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

Thoma states that this volume was written to describe in detail special work in a special field and particularly to correlate the pathologic changes that are encountered in that field with the clinical expression of disease. This aim has been accomplished most successfully.

Diseases of the jaw are discussed from a variety of angles: Malformations, fractures, infections, endocrine disturbances and tumors, benign and malignant, primary or metastatic, are depicted as they involve the jaw. Each phase of diseases of the jaw is well described clinically and pathologically; brief reports of cases are frequently interpolated and help to enliven the text; the illustrations are clear and helpful, and at the end of each chapter are those references to the literature which the author considers most significant in regard to the topic under discussion.

A wealth of material has been analyzed and sorted out to make up this book. Thus the volume as a whole is very complete. Surgeons, internists, radiologists and dentists will find much of common interest in it and will be glad to have it on hand for reference in their attack on the many diverse clinical states that may involve the jaw.

Hygiene for Freshmen. By Alfred Worcester, A.M., M.D., Sc.D. Price, $1.50. Pp. 151. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

The business of teaching hygiene, that is to say, elementary medicine, to laymen is at best a difficult matter. How shall one make the subject at all intelligible to those who have not the underlying scientific knowledge? How shall one preserve a proper balance so as not to create perplexities, doubts and phobias? How avoid the danger inherent in "a little knowledge"? The present compendium seems to achieve its end fairly well within these limits. Two sections, however, stimulate the reviewer to make certain comments. The teaching of the hygiene of exercise is cautiously worded so as not to conflict too blatantly with the obviously unhygienic practices tolerated in certain branches of athletics. One finds no comment on whether it is good or bad for the body and mind to have young men pounded and beaten on the football field or to have them collapse over their oars at the end of a boat race. The statement is merely made that "No boat race can ever be won by a crew just after dining." So, too, in the passages on sex hygiene, one discovers under an outer show of frankness the same old evasions. It is a question whether sex problems should be dealt with in books at all. The circumstances are different in each case and can be solved adequately only by individual conferences. At any rate, let one hope that some day this problem will be discussed with freshmen from the purely physiologic and medical standpoint without sinister and sanctimonious overtones.

Functional Disorders of the Large Intestine. By Jacob Buckstein. Price, $3. Pp. 265, with 60 drawings and 40 roentgenograms. New York: Harper & Brothers, 1934.

Buckstein has compiled a concise, readable review of the functional disorders of the bowel, which is enriched not only by a comprehensive bibliography but also by his own wide experience in this field. As in former works by this author, there are many excellent illustrations, particularly the series of roentgenograms. Details of diets and exercises, which in many books are left to one's imagination, are included.

The author has summarized various opinions on such subjects as ileal and cecal stasis, enteroptosis, intestinal flora and autointoxication. The text leaves one with the impression that such conditions may cause more trouble than is usually held by many workers in this field. It is regrettable that colonic irrigations for mucous colitis should be included in the discussion of treatment, although in another section routine irrigation is properly condemned. Probably for completeness, various types of diarrhea are included, but necessarily too briefly for the author to do them justice. In the discussion of sprue, for instance, mention of the use of liver in treatment has been omitted.

Leitfaden der einheimischen Wurmkrankheiten des Menschen. By L. Szídat and R. Wigand. Price, 15.50 marks. Pp. 212, with 156 illustrations. Leipzig: Georg Thieme, 1934.

This monograph, without claiming originality, deals in a concise and readable form with the common animal parasites of man and the diseases caused by them. The format is excellent, and the many splendid illustrations are an outstanding feature. The American reader, educated by the work of the Council on Pharmacy and Chemistry of the American Medical Association, is shocked at the emphasis placed on proprietary pharmaceuticals, such as filmaron, gelodurat, helminal, butolan, oxylax, oxymors, oxural and wurmserol. Owing to absence of an index, the book is difficult to use for reference.